

Malaria Sentinel Surveillance Site Assessment

Mekong Region
April 16-May 17, 2002

Abdelkrim Smine, Ph.D.
Senior Research Chemist
U. S. Pharmacopeia

USP Drug Quality and Information Program
(USP DQI)

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For more information, contact:

U.S. Agency for International Development
G/PHN/HN/HPSR
1300 Pennsylvania Avenue, N.W.
Washington, DC 20523-3700 USA
Phone: (202) 712-4789
Fax: (202) 216-3702
E-mail: aboni@usaid.gov



United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852 USA
Phone: (301) 816-8162
Fax: (301) 816-8374
E-mail: uspdqi@usp.org

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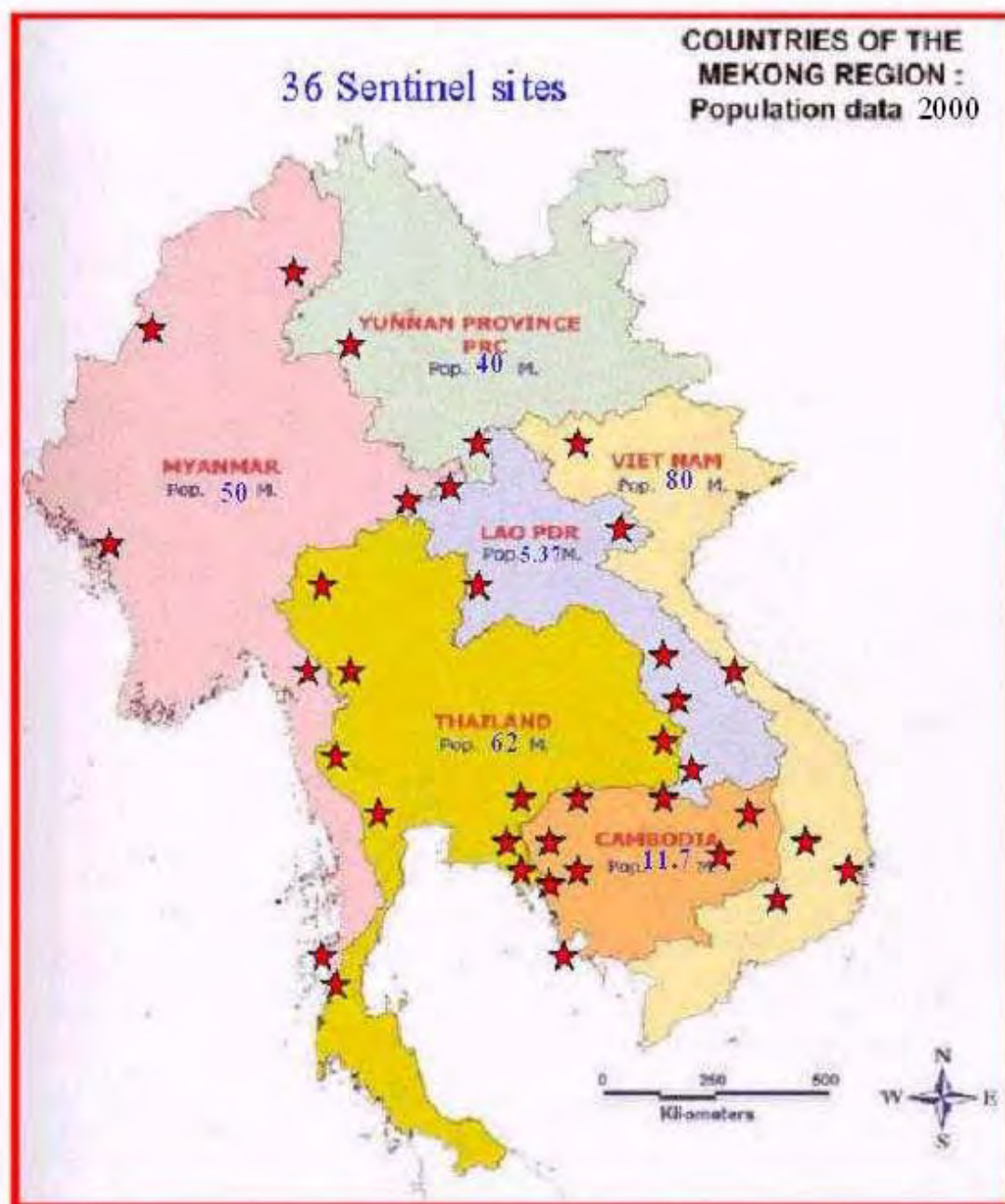
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Map of Sentinel Surveillance Sites



Acronyms

ANE	Asia/Near East Bureau of USAID
BASICS	Basic Support for Institutionalizing Child Survival
CA	Cooperative Agreement
CDC	Center for Disease Control, Atlanta
CEFOREP	“Centre de Formation et de Recherche en Santé de la Reproduction”
CFA	Unit of currency in Senegal
CMS	Community marketing services
DMM	Drug Management for Malaria
DMCI	Drug Management for Childhood Illness
DPM	Direction de Pharmacie et Médicaments
EDL	Essential Drug List
FDA	Food & Drug Authority
IMCI	Integrated Management of Childhood Illnesses
IPT	Intermittent Presumptive Treatment
ITN	Insecticide Treated Net
LNCM	“Laboratoire National de Contrôle des Médicaments”
MHFP	Maternal Health and Family Planning
MSH	Management Sciences for Health
NGO	Non Governmental Organization
OMS	“Organisation Mondiale de la Santé”
PAHO	Pan American Health Organization
PCIME	“Prise en Charge Intégrés des Maladies de l’Enfant”
PNA	“Pharmacie Nationale d’Approvisionnement”
PNLP	“Programme National de Lutte contre le Paludisme”
RBM	Roll Back Malaria
RPM Plus	Rational Pharmaceutical Management Plus
SNAN	“Service National de l’Alimentation et de la Nutrition”
SNEPS	“Service National de l’Education pour la Santé”
SNGE	“Service National de grandes endemies”
SNSP	“Service National de Santé Publique”
SNSR	“Service National de Santé de la Reproduction”
SP	Sulfadoxine-Pyrimethamine
SSP	“Soins de Santé Primaires”
USAID	United States Agency for International Development
USPDQI	United States Pharmacopeia Drug Quality and Information
WARO	West Africa Regional Office (BASICS)
WHO	World Health Organization
WPRO	Western Pacific Regional Office

Executive Summary

Background

Southeast Asia has a long history of malaria, cycling from epidemics brought under control with antimalarial drugs only to have new, drug-resistant strains emerge. During the past decade, however, new strains of the particularly virulent form of *P. falciparum* have developed resistance to most first- and second-line antimalarial drugs in circulation.¹ The Mekong Roll Back Malaria Initiative, established in March 1999, identified this as a major concern in the high mortality rate and growing costs of treatment. This situation presents an added threat to the population of the Mekong region for whom malaria continues to be a major health problem.

Drug quality and control has been determined to be one of the factors contributing to the growing resistance to antimalarial drugs. Successful treatment of malaria relies upon proper diagnosis and adherence to the protocol for malaria treatment, including completing the entire regimen of prescribed drugs. With partial or improper therapy, malaria parasites remain that build tolerance to the drug; increased exposure to antimalarial drugs results in increased resistance. Decreasing effectiveness of anti-malarial drugs to treat *P. falciparum* malaria in this region has prompted USAID, the World Health Organization (WHO), Roll Back Malaria, and USP DQI to examine drug quality as a possible contributing factor to resistance. Substandard products may deliver an improper dose of the antimalarial drug, allowing the parasite to survive and develop resistance.

Substandard drugs can be found in a variety of forms. A substandard product is a legally branded or generic product, but one that does not meet international standards for quality, purity, strength, or packaging. To be considered “substandard” a product could:

- Contain no active ingredient, but harmless inactives;
- Contain harmful or poisonous substances;
- Not be registered, or have been manufactured clandestinely, or smuggled into the country and thus be on sale illegally;
- Have been registered inadvisably by a weak agency; or
- Have passed its expiration date.

A counterfeit or “fake” drug is one that has been deliberately mislabeled for identity and/or source. It could be a perfect imitation containing the same active ingredients, same formulation, and identical packaging.

In recent studies conducted in the Mekong countries,² over 30% of drug samples marked “artesunate” collected from shops in Cambodia, Laos, Myanmar, Thailand, and Vietnam, actually contained no active ingredient; other preparations contained less than 25% of their stated ingredient. Use of fake or substandard antimalarial drugs is apparently widespread, primarily along the Mekong countries' border regions – among the highest at-risk population – where they

¹ Partnerships for Monitoring and Community-based Response to Multi-drug Resistant Malaria along Thai Border Areas, The Kenan Institute, Asia; March 3, 2000; p.1

² Paul Newton et al., “Fake artesunate in southeast Asia,” *The Lancet*, 357 (2001):1948

are sold on the open market. The migratory nature of the population, poor access to health facilities, and financial constraints each play a role in exacerbating the problem of multi-drug resistance.

Recognizing the need for a coordinated approach, the World Health Organization Western Pacific Regional Office (WHO/WPRO) convened an “Informal Consultation on Monitoring Resistance to Antimalarial Drugs in the Mekong Region” in Phnom Penh, Cambodia, October 2000. Representatives from six Mekong countries, partners of the Roll Back Malaria Initiative, members of research institutions, and the WHO Secretariat met to strengthen the coordination and inter-country cooperation on monitoring resistance to antimalarial drugs in the Mekong region. In that meeting, participants:

- Formulated a minimum package of standardized methods to be used at sentinel sites, as well as several complementary testing, assessment, and surveillance options. (The Mekong countries committed to implementing the essential minimum packet of standard monitoring methods.)
- Established a balanced, epidemiologically representative network of 36 sentinel sites, taking into account major population movements, border areas, high drug pressure, and known hot-spots of drug resistance.
- Developed ways of building essential capacities by inter-country collaboration, made plans for training related to the resistance surveillance network, and committed partners to financial support.
- Agreed upon rapid, general sharing of surveillance data, and improved country-to-country and site-to-site communications.

A partner in the Roll Back Malaria Initiative, USP DQI has focused its efforts on improving the quality and quality control of antimalarial drugs, maximizing the expertise of U.S. Pharmacopeia resources. This reports documents a trip to the Mekong region by USP DQI representative Abdelkrim Smine, Ph.D., to assess the capability of country-selected drug resistance sentinel surveillance sites to add the function of antimalarial drug quality control. The long-term goal of drug quality control in this context is to increase treatment efficacy, reduce drug resistance, and maximize the use of health care resources for malaria.

Drug quality monitoring by a subset of sentinel surveillance sites is one component of the antimalarial drug quality assurance strategy developed by USP DQI and WHO/WPRO for the region. This strategy also includes:

- ◆ Implementing quality control in new drug development processes ;
- ◆ Introducing Good Manufacturing Practices (GMPs) for production;
- ◆ Strengthening capacity of national drug quality control laboratories;
- ◆ Improving documentation of drug quality test results;
- ◆ Analyzing data on both drug quality and drug use practices;
- ◆ Disseminating effective information; and
- ◆ Establishing a regional network for surveillance.

In cooperation with WHO, Dr. Smine traveled to five countries of the Mekong region to assess the ability of the country-selected sentinel surveillance sites to perform quality testing of antimalarial drugs. Dr. Smine reviewed each country's treatment guidelines, preventive measures, drug distribution system, and manufacturing practices to evaluate the quality and accessibility of malaria drugs. Dr. Smine, generally escorted by a WHO representative and a country official, visited government facilities, manufacturing laboratories, hospitals, and clinics in urban areas, and at the district and community levels.

The information collected covers a wide range of subjects, including: public health management structure and policies, malaria diagnosis procedures, laboratory resources and personnel, drug analysis test methods, drug resistance monitoring, data reporting, drug distribution, counterfeiting, border trade, and drug certification and registration. The evaluators attempted to determine how Mekong countries might identify factors that contribute to the spread of malaria, how those countries might benefit from USP DQI involvement, where USP DQI might introduce Good Manufacturing Practice (GMP) guidelines, and how to share USP methods for carrying out quality drug tests.

Objectives of the Visit

In the Mekong countries of Cambodia, Laos, Thailand, Viet Nam, Burma, and the Yunnan Province of China, malaria is a serious public health problem. USPDQI examined the national malaria control program (NMP) in five countries in order to:

1. Learn about the current situation in the country, the number and scope of treatment facilities, and treatment guidelines.
2. Determine what the Division of Drug Analysis, Ministry of Health, Thailand needs to function effectively as an international center for antimalarial drug analysis as identified by WHO. This visit was a follow-up to the first assessment done by USP in November 2001.
3. Assess the capacity of two selected sentinel sites in the border areas of each country to function as regional drug quality control points.
4. Provide specific recommendations for training and/or equipment purchases necessary to enable the sites to perform effectively.
5. Collect a small number of antimalarial drug samples from various sources to be used only in the USP laboratory to develop the analytical methods.

Overall Recommendations/Next Steps

Additional detailed findings and more country-specific recommendations are included under the individual country reports.

1. USP DQI must develop appropriate testing methods (thin layer chromatography and/or colorimetric) to be used by the sentinel sites.
2. USP DQI must develop a Training of Trainers (TOT) program and determine the type and amount of materials needed to procure for the training.

3. Sites recommended initially for development as drug quality control points include:
 - China: Mengla and Ruili Counties, in their respective Institutes of Parasitic Diseases where drug resistance is being monitored.
 - Cambodia: Battambang City Hospital, Pailin City Hospital
 - Viet Nam: Lai Chau (North), Khan Hoa (South), plus one site in the central zone
 - Thailand: Kanchanburi Vector Borne Disease Control Center, Chantaburi Vector Borne Diseases Center, and Songkhlaburi District Hospital or Vector Borne Diseases Center
 - Laos: Savanakheth Malaria Center and Phalanxai District Hospital
 - Burma: Sites still to be selected
4. Identify two persons from each site to be trained as trainers in rapid testing methods.
5. The following drug quality control labs are recommended to serve as reference labs for the sentinel sites:
 - China: Kunming Provincial Laboratory at the Center for Disease Control
 - Cambodia: National Laboratory for Drug Quality Control
 - Viet Nam: National Drug Quality Control Lab
 - Thailand: Division of Drug Analysis, MOH, Bangkok
 - Laos: Food and Drug Department National Laboratory
6. Plan collaboration with local manufacturer to produce simple test kits, probably in Yunnan.

To provide needed research, USP DQI, WHO Cambodia, the Cambodian National Laboratory for Drug Quality Control (NLDQC), and the National Malaria Center should collaborate in conducting an antimalarial drug quality survey to determine the relationship of drug quality to drug resistance. This study would not require major investment. USP DQI can design the sampling and testing procedures in collaboration with the NCL, and purchase the drugs and reagents. WHO can arrange for drug collection from high-risk and border areas. NLDQC can conduct the drug analysis. This study will also raise awareness among other Mekong countries. It was clear from the discussion at the ACTMalaria meeting (April 23, 2002, Malaysia) that drug quality is still perceived as a minor issue within the RBM program in the Mekong. Discussion is also underway with Wellcome Trust and CDC about a multi-country collaborative study that could include Cambodia, Laos, and Thailand.

7. To improve Good Manufacturing Practices (GMPs), USP should:
 - Visit the Cambodia Pharmaceutical Enterprise and assess their GMP improvement before they start any production, but after they finish the stability and bioavailability studies. WHO and all local authorities are requesting USP DQI's assistance with this.
 - Invite representatives of four institutions in Viet Nam to visit USP for a weeklong training in lab GMPs. (National Control Lab, sub-Institute in Ho Chi Minh City, and the directors of the provincial drug quality control labs in Lai Chau and Khan Hoa). Viet Nam is interested in upgrading their labs and manufacturing plants to meet international GMP standards.

- Provide technical assistance to local manufacturers in Laos for achieving GMPs. The Ministry of Health plans to help at least three national factories improve their manufacturing practices this year.
 - Work with Hollykin, the Chinese company that plans to manufacture Artekin™ (dihydroartemisinin + piperaquine) in Cambodia, to ensure that the factory GMPs are acceptable.
8. Plan collaborative development of reference standards for artemisinin-based antimalarial products with China and/or Viet Nam.
 9. We support using the Division of Drug Analysis, MOH Thailand as an international center for antimalarial drug control in Southeast Asia. Before that can take place, however, the DDA laboratory staff would need to be trained in good laboratory practices, and many standard operating procedures needed to meet GMP would have to be issued and implemented. The same is true for the staffs from the regional medical science centers.
 10. There is no drug quality control program in place in Laos, but one is greatly needed because the quality of drugs on the market is very poor. Priority should be given to improving the Food and Drug Department Laboratory (FDDL). This lab requires additional resources and broad-based training. The FDDL staff would best benefit from learning how to perform drug testing using simple methods, so that they can serve as trainers to FDD staff in the provinces and districts. WHO should provide support for the lab to acquire staff and equipment.

USP DQI
Sentinel Surveillance Site Assessment
Yunnan Province, China, April 16-19, 2002

General background

Yunnan Province is located in southwest China, a mostly mountainous area of 382,000 km². The southern and western parts of the province share a 4,060 km border with Vietnam, Laos, and Myanmar. The climate is subtropical with distinct dry and rainy seasons. The total population of Yunnan province is 41 million; about one third of the population is made up of minority groups. Yunnan is divided into 16 prefectures, which are further divided into 127 counties. Thirteen percent of the provincial population lives in 25 counties (from eight prefectures) in border areas. The gross domestic product (GDP) in the border areas is 2,580 yuans (about \$312.00 US). The sentinel surveillance sites selected for this assessment were Mengla and Ruili: Mengla is a county in Xishua Banna prefecture; Ruili is a county in Dehong prefecture.

Organization:

Province→ Prefecture→County→Township→Administrative village→Natural village

Sentinel surveillance sites:

- Lingcang Prefecture
- Honghe Prefecture
- Yuxi Prefecture
- Simao Prefecture
- Xishuangbanna Prefecture
- Dehong Prefecture

Malaria remains a public health problem in Yunnan only at the borders with Laos, Vietnam, and Myanmar. Recently, malaria incidence has remained static except for a fluctuation in 2001 – a decrease, where the incidence remained low and static – that supposedly was related to weather change. Xishuan Banna prefecture where malaria is endemic has adopted and started the Roll Back Malaria (RBM) project in early 2001. Therapeutic efficacy studies and *in vitro* studies were regularly carried out in Mengla County of this prefecture. Due to the tight schedule, the team was only able to visit Mengla County and skipped Ruili County, which borders Myanmar.

In general, malaria diagnosis and treatment is provided to the majority of cases by the government, from the county level down to villages. All antimalarial drugs prescribed came from the same sources, i.e., manufactured by the government. Private hospitals, private clinics, and private drug stores also use the same drugs. There is an existing system to conduct quality control of drugs, including antimalarial drugs, but this requires strengthening. The quality assurance (QA) facility we visited in Mengla City does not appear to be performing authentic drug tests. The issue of drug QA is one of government priorities, as noticed from the recent establishment of the Drug QA section at the Public Health Bureau. Regarding rapid tests (thin

layer chromatography (TLC) or colormetric) for detection of fake or substandard drug products, the township hospital is the lowest level where rapid tests can be properly used.

The team did not visit any of the pharmaceutical companies that are located in Kunming, the capital city of Yunnan Province. Overall, all government officials at all levels showed strong interest in strengthening antimalarial drug QA in Yunnan Province. Field tests of antimalarial drugs could be implemented easily in sentinel sites where drug resistance is being monitored. A visit by USP DQI to Kunming pharmaceutical companies that are manufacturing antimalarial drugs should be planned in collaboration with WHO-WPRO in the near future.

Meeting during Mekong Basin Disease Surveillance Project (MBDS) Conference,

Kunming, China, April 16

Participants: Dr. Abdelkrim Smine, Research Scientist, USP DQI
Dr. Krongthong Thimasarn, WHO Medical Officer, Roll Back Malaria-Mekong
Dr. Allan Shapira, Regional Advisor, WHO/WPRO
Dr. Alan Schnur, WHO-Beijing staff
Dr. Zhang Zaixing, Director of Malaria Control Program, Director of Yunnan Institute of Parasitological Diseases

Dr. Smine presented information about the USP DQI program and how it will proceed in China and the other Mekong countries. Drs. Schapira and Schnur cautioned Dr. Smine that USP DQI should collect only a few tablets and that nothing about the drugs' quality should be discussed or published, otherwise the Yunnan government might not collaborate with USP DQI in future projects.

Chloroquine, quinine, and artesunate are all used to treat malaria and are available in private pharmacies. All could be purchased without prescription.

Dr. Shapira proposed that USP DQI include injectables in the drug quality assessment. He also suggested that the health officials who are already working on drug resistance monitoring should be involved in drug quality program, since they have the time, the knowledge, the funds and work in both Mengla and Ruili sites. Dr. Shapira advocated visits to hospitals and other institutions, but without losing sight of the objective: to run screening tests in more remote areas.

Dr. Smine explained that USP DQI would be assessing the ability of these sites to perform the quality testing of antimalarial drugs. In Yunnan, reagents and other lab equipment appear to be readily available. A question arose about the possibility of developing a "ready to use" kit. Dr. Shapira and Dr. Zhang believed that this could be done in Jinhong, and Dr. Zhang's supervisor supported the idea. USP DQI should consider how to collaborate with a qualified private company to produce a simply designed, easy-to-use test kit.

Later, Drs. Thimasarn and Smine met with Dr. Eva-Maria Christophel, WHO-Laos, and the malaria teams from Thailand and the Philippines who were also attending the MBDS Conference.

Jinghong (Xishuang Banna), China

Meeting with the Public Health Bureau of Jinghong, April 17

Participants: Dr. Abdelkrim Smine, Research Scientist, USP DQI
Dr. Krongthong Thimasarn, WHO Medical Officer, Roll Back Malaria-Mekong
Dr. Li Huanxian, Associate Professor and Chief for Information Management,
Yunnan Institute of Parasitic Diseases (YIPD)
Dr. Yang Henglin, Director of Parasitic Resistance Division, Mengla (Xishuang
Banna prefecture on the Laos border), Ruili (West Yunnan, Dehong
prefecture on Myanmar border), and Honghe prefecture (Vietnam border)
Dr. Yang, Epidemiologist and Deputy Director of Public Health, Xishuang Banna
Dr. Dai, Director, Roll Back Malaria and Drug Quality Issues, Yunnan Province

Malaria in Yunnan Province

The malaria control program begun last year in Mengla continues to follow the Roll Back Malaria guidelines. In Xishuang Banna prefecture, 1,389 cases of malaria were reported in the year 2001 (in vitro and in vivo confirmed cases) in a general population of 860,000. Of those cases, 430 are *P. falciparum*. There were only three deaths in remote border areas due to aggravated cerebral malaria; the cases were non-Chinese, however.

Prevention

Chloroquine and primaquine are used for prophylactic treatment; sulfadoxine-pyrimethamine (SP) is distributed only to the high-risk population. The SP is produced locally in the People's Republic of China with different combinations from the original Fansidar® (i.e., sulfadoxine 250 mg. + pyrimethamine 17.5mg.). The dosage for prophylaxis is 2 tablets/week or 4 tablets/month.

Treatment guidelines

Treatment for *P. falciparum*

Treatment is a combination of primaquine 7.5 mg/tablet with one of the following:

- Artesunate 50 mg
- Artemether 50 mg
- Dihydroartemisinin 20 mg
- Pyronaridine 100 mg

Treatment for *P. vivax*

- Chloroquine
- Primaquine (Used for prophylaxis when *P. vivax* is the main vector)

Drug Resistance Monitoring

The Yunnan Institute of Parasitic Diseases (YIPD) monitors drug resistance once every three years in border areas, and once every ten years in central areas. Resistance of *P. falciparum* to chloroquine and sulfadoxine-pyrimethamine was reported as early as 1965. Between 1991 and 1995, resistance of *P. falciparum* to chloroquine, amodiaquine, and SP was more than 90%, as reported by Mengla, Ruili, and Honghe surveillance sites. In Mengla, *P. falciparum* is resistant

to artesunate and dihydroartemisinin by over 12% when they are taken alone, but showed no resistance to mefloquine and quinine. *P. vivax* is still sensitive to chloroquine.

The government controls the manufacture and quality of all antimalarial drugs used within China. Information on poor quality drugs is communicated to all other health facilities in the province. Compared to other Mekong countries, malaria is not a major health problem in Yunnan, and the quality of antimalarial drugs appears to be good. Dr. Henglin, who is responsible for monitoring resistance and drug efficacy in the province, will oversee the drug quality testing. His division boasts a qualified staff and he is in charge of all the prefectures in the province, including three border sentinel surveillance sites. This will allow USP DQI to work directly with the Yunnan Institute for Parasitic Diseases.

Field Trip to Xishuang Banna and Mengla

Participants: Dr. Abdelkrim Smine, Research Scientist, USP DQI
Dr. Krongthong Thimasarn, WHO Medical Officer, Roll Back Malaria-Mekong
Dr. Li Huanxian, Associate Professor and Chief for Information Management,
Yunnan Institute of Parasitic Diseases (YIPD)

The area between Xishuang Banna and Mengla is mountainous, very green, hot and sub-tropical, but not yet rainy. We visited a historical village about 20 miles from Xishuang Banna and a village called Monglay, which is comprised of about 400 residents. We met with the local doctor, who was trained by the government and by the Malaria Institute. His small clinic consists of a small pharmacy, with a reasonable drug supply, and six patient beds. Almost all antimalarial drugs were available, and we collected sulfadoxine-pyrimethamine (SP), chloroquine, and primaquine.

We visited a second village hospital about 60 km from Jinghong. This private clinic, sponsored by the government, is run by a doctor who has worked the government for many years in the field of malaria. He still performs malaria prevention work for the prefecture of Mengla. His clinic has a small pharmacy, well equipped with essential drugs. He was trained by the Malaria Institute to perform blood smears and has a small microscope to determine which strain of malaria his patients have before prescribing treatment. Malaria cases are very rare in this season – he averages only two malaria patients a month – but that number will increase around August. Government guidelines on malaria treatment, drug regimens, drug storage and handling, and precautions for pregnant women and children are clearly posted on the clinic wall. After training by Dr. Lixuan and with use of necessary office equipment (electricity, telephone, fax), this small clinic could easily conduct simple drug analyses.

Meeting at the Public Health Institute of Mengla, April 19

Participants: Dr. Abdelkrim Smine, USP
Dr. Krongthong Thimasarn, WHO
Dr. Yang Henglin, YIPD
Dr. Li Huanxian, YIPD
Dr. Yang Jihong, Associate Professor and Chairman, Public Health Bureau
Mengla County
Dr. Jiang Yun Chun, Director of Anti-epidemic Division, Mengla County

Dr. Liu Hua Xing Deputy Director and Assistant to the Chairman, Anti-epidemic Division

Dr. Xiao Yu Jiang, Deputy Chief, Parasitic Control Division

Dr. Yang Xueli, Pharmacist and Deputy Director, Drug Surveillance Bureau

Dr. Li Hong Bin, Chief, Parasitic Control Division

We took a field trip to Xishuan Banna prefecture, where we met with health officials on the prefecture level in Jinghong City. From there, we traveled to the county of Mengla and worked with health officials of the Yunnan Institute of Parasitic Diseases in Mengla City.

The chairman updated us on the malaria situation in Mengla County. In the year 2002, there were 718 cases of all communicated diseases, 507 cases of which were malaria cases (or 60% of the total). Of these, 402 cases were caused by *P. vivax*; 105 were caused by *P. falciparum*. It is evident from these numbers that malaria is a major health problem in this county and that infection by *P. vivax* accounts for the majority of the cases.

The total population of Mengla County is 234,500, primarily minority groups; about 60,000 persons live in Mengla City. The county has 13 townships and 71 villages and shares a 740 km border with Laos and Myanmar. The area is mountainous, with a tropical climate and a rainy season that lasts from May to November. Malaria cases are highest during the rainy season.

Malaria control and management

The Public Health Bureau of Yunnan Province has three different divisions at the same level:

- Parasitic Diseases Control (YIPD) headquarters in Simao City;
- Epidemic Disease Control in Dali City; and
- Center for Disease Control (CDC) in Kunming (the capital of Yunnan Province).

The Mengla Institute, which we visited, is part of YIPD.

The Public Health Bureau has a malaria management program which implements Roll Back Malaria guidelines. These are being followed throughout the province in both the public and private sectors:

- Continued monitoring of vector resistance;
- A prevention program enforced in high risk population; and
- A reporting network of data about malaria cases from village to township to county to prefecture to province level.

The YIPD assures the training of staff; in fact, one of Mengla County YIPD's main activities in the 2001 RBM program was to train staff at the township level. The township staff, in turn, trains staff at the village level. Training topics cover health promotion, malaria prevention/drug prescription, and data collecting and reporting.

Diagnosis

All 13 township hospitals within Mengla County have microscopes, all are run by malaria-trained doctors, and all perform blood smears on every malaria patient. The doctors also

collect data from village hospitals and report it to the county on the 5th, 15th, and 25th of each month. Only five village hospitals have microscopes.

Prevention

The prevention program is administered based on one of three malaria risk factors:

- In areas with more than a 10% malaria incidence, prevention measures are taken for the entire population, that is, spraying with deltamethrin 5% three times a year between July and September.
- In areas with a malaria incidence between 5-10%, prevention measures are given only to people with a history of malaria; they are sprayed one to two times between July and September.
- In areas with less than a 5% malaria incidence, prevention measures are given only to the population with a repeated history of contracting malaria.

Peaks of malaria incidence are observed – some peaks have occurred as late as November in some areas – and prevention and spraying are adjusted accordingly. The same program is implemented throughout the province.

Prevention treatment

- Chloroquine, piperaquine, and SP (for high risk)
- Artesunate are not given for prevention due to their high cost and short life.

Treatment guidelines for Yunnan Province

- *P. vivax* is treated with chloroquine, primaquine, and quinine.
- *P. falciparum* is treated with artesunate (tablet for less serious cases, injections for serious cases), and arthemeter.
- Drug combination treatments are being studied.

Facilities Visited, Human and Material Resources

- Yunnan Institute of Parasitic Diseases and the Mengla City Hospital

We first visited the drug quality control division, which is charged with checking drug quality. It consists of four units: Chemical, Biological, Traditional, and Administrative. Dr. Yang Xueli, Pharmacist and Deputy Director of the Drug Surveillance Bureau, is the chief of the division; he supervises three additional pharmacists and four staff members. The drug quality control division does not perform all drug analysis tests required by the official monographs. The only pharmacopeia we saw was the Chinese Pharmacopeia, and the head of the division seemed not to be very familiar with testing antimalarial drugs even using that book. This division, however, is more than qualified to do basic drug testing using simple methods: All common reagents are present; the lab contains a UV spectrophotometer, microscope, pH meter, precision balances, and suitable work bench; and the facility has telephone, fax, computers, and internet access. The staff members are trained pharmacists, qualified to do the testing after appropriate training.

- **The Hospital and Hospital Pharmacy**
New and very modern, the pharmacy is very well maintained, with all types of antimalarial drugs present. We collected chloroquine phosphate 250 mg (made in China), arthemeter (made in Kunming, China), and artesunate tablets (made in Guilin, China). The pharmacists were very knowledgeable about antimalarial drugs and expiration dates; expired drugs are melted.
- **Visit to the Blood Work Lab**
The lab consists of four rooms and there were more than three staff members doing lab work, mainly liver function and parasitic analyses. This lab is run by the YIPD. Dr. Henglin performs the blood work on all malaria patients in this facility; he also trained the staff working here.
- **Visit to a Private Pharmacy in Mengla City**
This pharmacy was also very modern. All antimalarial drugs are available and the government malaria guidelines are posted on the wall. There is a complaint desk to allow clients to report any problems with any given drug and complaints filed are investigated. We collected artesunate and arthemeter from this pharmacy.
- **Visit to a Public Pharmacy in Mengla City**
The public pharmacy is as modern and well equipped as the private pharmacy. The antimalarial drugs we checked are exactly the same as those we saw in the hospital and the private pharmacy. The difference lies in the management: The government owns the public pharmacy and the prices of the drugs are fixed, while a pharmaceutical company may own the private pharmacy and it cannot fix drug prices. The same regulations concerning the purchase, quality, and sale of drugs apply to both sectors.
- **Visit to a Small Private Clinic**
A retired doctor, who previously worked on malaria in the public hospital, owns this small clinic. He said that he sees very few malaria cases. He had antimalarial drugs on hand, such as arthemeter, but we also found an expired quinine blue pack, made in Thailand in 1996. Dr. Thimasarn told me that the manufacture of that drug was discontinued, as quinine blue seems to have no effect on malaria.
- **Visit to a Private Clinic**
On a quick visit to the clinic's pharmacy, we found all the antimalarial drugs as we found in other places. We learned here that patients must pay for their health care, whether it takes place in either the public or private sector. If they cannot afford to pay at the time of their visit, they are expected to pay the costs back later.
- **Visit to a Village Hospital**
There is a village hospital with four beds about seven miles from Mengla City. The clinic is run by a couple with three years of medical school training. They receive a small stipend from the government but, as a condition to running the private hospital, they are required to do some work for the malaria control program. There were very few patients at this time of the year and they send all complicated cases to Mengla Hospital.

- Visit to a Township Hospital

On our way back to Jinghong, we visited a township hospital. It had 14 doctors, 19 other staff, and a small lab equipped with a microscope, a refrigerator, two incubators, a small spectrophotometer, and chemical reagents. Part of this 34-bed hospital is new, a modern building with surgery and emergency rooms. We also visited the hospital pharmacy, which is very modern and stocks all antimalarial drugs, including the quinine, piperazine, and chloroquine we collected. We checked the hospital's data collection and reporting and found that it was updated daily. This hospital receives data about malaria cases from the villages, which is then added to the hospital data and reported to Mengla County on the 5th, 15th, and 25th of each month. All malaria cases are confirmed with blood smears. Other diseases are being monitored as well. With appropriate training and equipment, this hospital is well suited to carry out TLC testing.

Recommendations/Next Steps

1. After USP DQI develops appropriate testing methods, Dr. Zhang Zaixing, Director of Malaria Control Program and Director of YIPD, should choose two YIPD staff members to be trained as trainers (TOTs) in TLC. The two TOTs then will train the staff in Mengla and Ruili, where there already is a continuing training program in place.
2. USP DQI should supply necessary equipment for TLC training and implementation (what little is needed).
3. USP DQI should evaluate the provincial drug quality control lab in Kunming as a potential reference lab.
4. USP DQI should collaborate with China – YIPD, manufacturers of antimalarial drugs in Yunnan, and WHO – on the development of reference standards for artemisinin-based antimalarial products.
5. Yunnan appears to be the best place to produce any simple test kit we may develop. Dr. Zhang and his supervisor both said that the pharmaceutical companies are willing to work with us. He agreed to establish the contact and initiate collaboration between USP and Yunnan manufacturers.

USP DQI
Sentinel Surveillance Site Assessment
Cambodia, April 25-May 1, 2002

General background

The kingdom of Cambodia is situated in the southwest portion of the Indochina Peninsula, bordered by Thailand, Laos, and Viet Nam. The country is 181,232 km² with a population of 11 million inhabitants, a density of about 58 Cambodians/km². The country is divided into 24 provinces, which are divided into districts that are subdivided into communes. The health system is organized into province and operational districts (OD), with each OD comprised of many health centers and health posts. Sixty per cent of the Cambodian landmass is thinly populated forest and hilly areas, characteristic of malaria vector habitats with high malaria transmission but with little or no access to the public health system.

There are eight country-selected sentinel surveillance sites in the country. USP DQI visited two sites in the northwest of the country close to the Thai border. The first site, Sampoevlun in the province of Battambang, is about 120 km from Battambang City. The second site, Pailin City, is a province level site. Between 1975 and 1997, the entire area between Battambang and the two sentinel surveillance sites was a war zone. Local Khmer people, returning refugees, new settlers in the forested ex-Khmer Rouge area, and trans-seasonal forest workers, populate the area. The ravages caused by more than 20 years of war and the nature of the population make these two provinces high-risk areas for malaria.

Country-selected sentinel surveillance sites:

- Kratie province
- Battambang province
- Pursat province
- Sihanouk Ville
- Mondulkiri province
- Treng province
- Kg Speu province
- Rattanakiri province

Meeting with WHO Staff, Phnom Penh, April 25

Participants: Dr. Reiko Tsuyuoka, Scientist for Malaria Control, WHO
Dr. Jim Tulloch, WHO Representative, Cambodia
Dr. Abdelkrim Smine, Research Scientist, USP DQI

Dr. Smine briefed the WHO officials on the objectives of the trip and asked about the malaria situation in Cambodia. He advised USP DQI to use caution in selecting individuals to be trained to conduct drug testing in the sentinel sites, and to consider the possibility of using blind samples to prevent any data tampering.

Visit to the National Drug Control Laboratory, April 25

Participants: Dr. Reiko Tsuyuoka, Scientist for Malaria Control, WHO
Dr. Nam Nivanna, Director, National Drug Control Laboratory
and two of his lab chiefs

USP DQI previously visited the National Drug Control Laboratory (NDCL) in November 2001.³ The NDCL conducts drug analysis, as requested by the Ministry of Health, for registration of new drugs, for quality control and, occasionally, for specific surveillance of suspected quality problems. Dr. Nivanna explained that the lab had just finished drug analysis of selected antibiotics and other drugs in the market (see attached list) and found that more than 13% of the drugs were fake. For instance, 80% of dexamethasone samples failed the tests; no antimalarial drugs were included. Counterfeit drugs continue to be a major problem in this country and, even though registration is required for imported drugs, many unregistered drugs are sold freely on the market.

Thirteen pharmacists and 23 technical staff work in this laboratory. It appears somewhat operational and the pharmacists demonstrated good knowledge about performing drug analysis according to major pharmacopeias. (A copy of the *USP24-NF19* was in use in the lab.) The lab lacks equipment needed to function fully (e.g., no calibrators for dissolution, only one HPLC with a single pump while the other is being repaired, etc.), but most of the basic drug tests can be performed.

Considering the drug quality issues and the abundance of substandard drugs in Cambodia, the National Drug Control Laboratory needs financial support as well as technical assistance to be able to play a major role in a national drug quality program.

Visit to Battambang Province, April 26

Participants: Dr. Abdelkrim Smine, Research Scientist, USP DQI
Dr. Reiko Tsuyuoka, Scientist for Malaria Control, WHO
Dr. Kheng Sim, National Malaria Center-Phnom Penh
Dr. Ros Seiha, National Malaria Center-Phnom Penh
Dr. Tol Bunkea, National Malaria Center-Phnom Penh
Dr. Heng Phirum, Supervisor, Malaria Control Program-Battambang Province

Malaria in Battambang Province

Battambang is the third largest city in Cambodia and one of the country-selected sentinel surveillance sites. The hospital in this city is considered a provincial hospital, or referral hospital. There are four health districts within the province: Battambang, Thmor kol, Sampoev Loun, Maung Russey. A total of 4,536 malaria cases were confirmed in this province in 2001 – 4045 cases diagnosed with blood smears, 491 with dipsticks. More than 80 % of the cases were *P. falciparum* malaria.

³ **Technical Support to WHO/WPRO Regional Malaria Control, Mission to China, Thailand and Cambodia, November 16 – 20, 2001.** P.Smith and N.Blum, USP DQI. December 2001.

Prophylaxis

Due to the cost of artesunate, the program does not support prophylaxis.

Treatment guidelines

Treatment of *P. falciparum* (throughout Cambodia)

- Artemether (or artesunate) + mefloquine
- Quinine + tetracycline

Treatment of *P. vivax* or *P. malariae*

- Chloroquine

The National Malaria Center provides referral hospitals and health centers with:

- pre-packaged blisters of artemether 50mg + mefloquine 250mg in a 3-day treatment regimen
- suppositories of artesunate (Plasmodin[®]) 50 mg for treatment of uncomplicated malaria in children between 6 months and 6 years
- Mefloquine and artesunate combination drug (Malarone[®]) and dipstick kits, with the support of the EC

Drug resistance

Drug resistance currently is tracked in Battambang Province and tracking is expected to start in Pailin Province with this year's rainy season. The National Malaria Center, with the support of WHO and EC, monitors drug resistance at four sites each year. Pailin was one of the sites selected for 2002.

Resistance of *P. falciparum* to mefloquine averages about 20% in these areas and cases of artesunate resistance were also reported, which is why WHO and National Malaria Center are providing combinations of mefloquine with artemether or artesunate. There are two major treatment behaviors in the population: The Khmer people have been in contact with malaria for a long time, so they tend to buy artesunate, store it, and use it when malaria symptoms occur. The rest of the population (mainly returned refugees and new settlers) wait until they get very sick before they seek treatment. Health officials worry that overuse of artesunate by the Khmer people may trigger the appearance of *P. falciparum* resistance to drugs that, to date, have been very effective.

Data reporting

All the hospitals, including private clinics, are expected to report malaria cases each month. The health posts and health centers report data to provincial hospitals. In every province there is a public health department (PHD) that collects all data – including malaria cases, drug resistance, and parasite types – and reports it to the National Malaria Center in Phnom Penh.

Facilities Visited

- Battambang Hospital

The Battambang Hospital laboratory performs blood smears for malaria cases among its patients and for samples sent by other health centers. Two pharmacists and

nine technicians run the lab, which is equipped with a microscope, centrifuge, and glassware. The lab has essential reagents that are distributed by the central medical store in Phnom Penh. A team from the National Malaria Center (a doctor, an epidemiologist, a pharmacist, and a lab technician) come here twice a year to check blood smears. The data reporting system in place is good and the records are up to date. **Drug quality control can be implemented here after appropriately training the staff and providing the lab with necessary, minor equipment.**

- Public Pharmacy of Battambang Hospital

Antimalarial drugs were present at the public pharmacy and we collected samples. We found artemether + mefloquine (the combination drug provided by the National Malaria Center), artemether injection, chloroquine, and quinine and the pharmacist demonstrated his knowledge of the treatment guidelines. In all public hospitals, malaria patients must pay for the consultation and blood smear, but the drugs are given free once the diagnosis is confirmed.

- Visit to a Private Pharmacy

The situation is different in a private pharmacy; it has all types of antimalarial drugs. We found different brands of artesunate, artemether, and other drug combinations. Many of the drugs are made in China (Kunming, Guilin, Chongqing, and Guangzhou). The drugs products available here were made by the same manufacturers of those found in Yunnan Province, only the packaging is different. The cost variation is very high among brands and the pharmacist did not appear to follow the national treatment guidelines.

- Visit to Rural Health Centers

We drove in two cars from Battambang City to S. Poevlun town (140 km). The road was very bad, the landscape forested and hilly; the weather was very hot, humid, and rainy. The area population, mainly new settlers, is scattered along the road. After the war ended in 1997, former inhabitants and refugees from other areas moved here; the newcomers burned forest trees and settled in, cultivating rice on small pieces of land. The area is very poor, however, there is some new development: schools and health centers have been built. We were told that this area was prosperous before the war. The primary economy seems to come from agriculture, rubber trees, and commerce in products smuggled from Thailand.

The first health center we visited, in the village of Ankurban, is 85 km from Battambang. We found available the drugs supported by the National Malaria Center, as well as chloroquine and blister packages of artemether and mefloquine (A+M) in tablets and suppositories. They use the dipstick method for malaria diagnosis, since they have no microscope. The data records are well maintained and indicated that, in the last three months, this center has had 71 confirmed malaria cases. The population of this village is estimated at 6,938.

Antimalarial drugs are provided free of charge at the health centers, but the patient must pay 1000 Rial (about \$ 0.25 U.S.) for the first consultation and 500 Rial for

subsequent consultations. Severe cases are sent to Poevlun or Battambang hospitals. **The center in Ankorban would not be suitable for conducting drug quality testing. The staff is not well trained and the facility is inappropriate for drug quality control.**

- Visit to Poevlun Operational District Hospital

This area is considered high risk both because of the landscape and the level of poverty. The laboratory here consists of two small rooms with electricity but no running water. Six technicians, trained in Battambang, run the lab and use blood smears to confirm malaria cases. WHO/National Malaria Center also uses this site for monitoring drug resistance. On average, about 400 patients with malaria symptoms visit this center each month; about 25% are confirmed malaria cases. Records show that *P. falciparum* accounts for 60% of malaria cases. The lab buys purified water from Thailand, but it receives other reagents from the central medical store in the capital once a month. There were also many organic solvents present. At the time of our visit, two staff members from the National Malaria Center-Phnom Penh were working here to check a new batch of dipstick kits recently purchased from an Australian-based company called Cellabs.

The lab staff is poorly trained, but the National Malaria Center's policy is to try to hire local Khmer to work here and train them gradually to perform basic tasks. **This site would not be appropriate for conducting drug quality testing in its present condition, due to the lack of skilled staff. The facility itself, however, could be used by the National Malaria Center (NMC) to conduct drug quality testing when NMC staff come here to work on drug resistance surveillance.**

- Sampoevlun Hospital Pharmacy

All the drugs sponsored by the malaria control program were present and we collected a few samples. (A list of drugs collected from each location is attached.)

Visit to the City of Pailin, April 27

Pailin is about 120 km west of Battambang. The landscape and population are similar to that of Battambang. The city of Pailin, just 15 km from the Thailand border, was very prosperous before the war because of its famous diamonds; in fact, people still come to the city to look for diamonds. The area is densely forested with a high incidence of malaria.

Facilities Visited

- Health Center, Village of Banan in Sdau commune, District of Rattanakmundul (halfway between Battambang and Pailin)

This health center serves only as an outpatient facility. We found the A+M combination treatment, chloroquine, quinine, and artemether injections. The health center follows the national treatment guideline here and diagnosis of malaria is made by blood smears. The National Malaria Center and WHO are trying to introduce a health education program within the primary and junior high schools of this village. The program will include malaria and Soil Transmitted Helminth (STH) diseases. STH affects 45% of the area's school children. WHO and the National Malaria Center have submitted a proposal to Japan International Cooperation Agency (JICA) for funding of this project. The National Malaria Center staff and WHO representatives asked if there were any

possibility to work with USP DQI to broaden the program, to develop the educational program, and to seek funding from other sources. (We will discuss this with Nancy.) **This health center would not be appropriate for drug quality testing.**

- Visit to the Provincial Hospital of Pailin

There is a public health department within the Provincial Hospital and the lab is very clean and well organized. The seven lab technicians have been trained three times by the National Malaria Center and they all can perform blood smears. Reagents provided by the central medical store are in stock. The hospital has typewriters and three new computers, with printers, used to store the data collection. Three health centers and one health post refer to this hospital. According to records, this hospital receives about 400 patients with malaria-like symptoms, 50% of which are confirmed malaria cases. Last year, 19 of the hospital's patients died of malaria. With a total population in the Pailin area of about 41,000, some 3000 malaria cases were reported; only 11 were caused by *P. vivax*.

- Visit to the Hospital Pharmacy

There is a large stock of all anti-malarial drugs. The pharmacy department receives drug supplies every three months. The pharmacist demonstrated knowledge of the treatment guidelines. The patients pay 10 Baht for consultation and get the anti-malaria drugs free of charge. Poor quality drugs have been reported in the city. It is said they come from neighboring Thailand and other areas. WHO and the National Malaria Center will start to conduct drug resistance surveillance at this site. **This site is well equipped and staffed to conduct drug quality testing.**

- Visit to a Private, Illegal Pharmacy

There are many illegal pharmacies in Pailin City. Health officials suspect a high percentage of fake drugs in this area because of border smuggling. We collected some artesunate made in Guilin, China, because the packaging is different from all the Guilin artesunate we found in Yunnan.

Meeting with Health Officials in the Malaria Program, National Malaria Center, April 29

Participants: Dr. Abdelkrim Smine, Research Scientist, USP DQI
Dr. Reiko Tsuyuoka, Scientist for Malaria Control, WHO
Dr. Stephan Hoyer, Coordinator, Infectious Diseases Control, WHO
Dr. Kim Sovann Yadany, Medical Officer for Malaria and Dengue, WHO
Dr. Sean Hewitt, Malaria Advisor, European Commission
Dr. Duong Socheat, Director, National Malaria Center
Dr. Khneg Sim, National Malaria Center

Dr. Smine presented the USP DQI objectives to the group. Dr. Socheat was satisfied with USP DQI's work in Cambodia and wants us to do more in order to help his country with the problem of fake drugs. Dr. Hoyer said that USP DQI should focus more on Cambodia, because fake drugs cause a lot of problems, not only for malaria control but for many other diseases. He asked that we return to visit the Cambodia Pharmaceutical Enterprise (CPE), because the plant was closed during this visit. He also mentioned that Hollykin, the company making Artekin

(dihydroartemisinin+ piperaquine) in Guangzhou, China, would soon build a modern facility in Cambodia to produce the same combination. Dr. Hoyer would like USP DQI to work with that company from the beginning to establish acceptable GMPs and drug quality controls. He, too, advised USP DQI to use caution in selecting individuals to be trained to conduct drug testing in the sentinel sites, and to consider the possibility of using blind samples to prevent any data tampering. WHO pays the National Malaria Center staff between 7.50 and 15 U.S. dollars a day when they are asked to carry out extra activities for the program. (The average salary of National Malaria Center staff is less than 20 dollars a month.)

All the participants expressed the need to combat fake drugs and agreed that an antimalarial drug quality survey would be a good initiative. The group also discussed AIDS cases and the news about global funds. The Cambodian AIDS control program received 15 million dollars over three years, but the malaria program was not funded. A second proposal for malaria and TB will be resubmitted.

Meeting with the Department of Drugs and Food, Ministry of Health, April 29

Participants: Dr. Abdelkrim Smine, Research Scientist, USP DQI
Dr. Reiko Tsuyuoka, Scientist for Malaria Control, WHO
Dr. Chroeng Sokhan, Vice Director

Dr. Sokhan explained the activities of his department and gave us an overview of the drug regulation in the country. He is very concerned with the problem of fake drugs and encourages any effort to help in this matter. He said that before 1970, drug laws and regulations in Cambodia were very well defined, implemented, and enforced. During that time, no drugs other than OTC drugs could be bought without prescription. A drug registration system did not exist, but no smuggled drugs were found in the market due to the absence of illegal drug shops. The licensing of private pharmacies started in 1988. After the war, everything had to be started from scratch.

Dr. Sokhan presented the latest data from a study, done with the support of WHO (the study we had discussed with the NDCL), that was designed and carried out in Cambodia. Some of the drug samples were tested in the Drug Analysis Division of the Thailand's Ministry of Health in Bangkok. The study covered 24 drugs, and confirmed the findings of the MSH study presented at the SEAM meeting last fall:

- The results showed that 13% of tested drugs failed to pass the tests.
- Counterfeits were found more among unregistered drugs.
- The registration system is effective and no substandard drugs were found among the locally produced ones.
- The problem of counterfeit drugs is a consequence of border smuggling and the presence of illegal drug shops in the country.
- Substandard products may be much higher than 13 % in areas near the borders and where no legal pharmacies exist.

Dr. Sokhan is trying to motivate other authorities to take an active role combating this problem of counterfeit drugs. He believes the same type of studies that examined the antibiotics market is needed specifically for anti-AIDS and antimalarial drugs. Dr. Sokhan also explained

Cambodia's drug regulations, and drug procurement and distribution systems, and reiterated that he will help us with anything he can.

Dr. Smine also met with Dr. Ngan Van Thon, a pharmacist with the National Malaria Center who is in charge of the drug surveillance in Phnom Penh. She presented many artesunate samples collected recently in the market. When tested in the national lab, these artesunates were found to have no active ingredients. The drug's packaging is a perfect imitation of the original artesunate from Guilin Pharmaceuticals in China. Dr. Van Thon was just beginning to distribute a large number of educational fliers about malaria to different areas in the country because the malaria high-risk season was about to start.

Conclusion

The Roll Back Malaria program is being well implemented in the public health system and the malaria mortality in Cambodia is decreasing. Malaria deaths went from 1,504 in 1992 to only 476 in 2001. Malaria incidence, in confirmed cases, ranged from 15.5 per 1,000 (1995) to 9.6 per 1,000 (2001). The main causes of malaria deaths in Cambodia are:

- The predominance and the resistance of the *falciparum* variety of malaria,
- The remoteness and inaccessibility of affected areas due to poor infrastructure,
- The abundance of fake and substandard drugs in the market, and
- The lack of qualified health workers, in the private sector specifically, and the lack of appropriate resources, in general.

Recommendations

1. There are three locations USP DQI recommends for initial drug quality control interventions:
 - Battambang City Hospital
 - Pailin City Hospital
 - Sampoevlun (with staff from National Malaria Center or other skilled health workers).

These locations were identified following the USP DQI assessment trip. Dr. Reiko Tsuyuoka (WHO) visited other sentinel sites in other provinces and completed the assessment questionnaire provided by USP DQI. Based on that information, the assessment team concludes that drug quality control could be established in all sites where drug resistance is being monitored, and that drug testing using TLC could be done at least in provincial hospitals. The selection and priorities of sentinel sites should be discussed with National Malaria Center and WHO staff.

2. After developing thin layer chromatography (TLC) methods, USP DQI should train staff from the National Control Laboratory and the National Malaria Center in its correct use. The National Control Laboratory has the needed equipment and the technical skills to perform TLC, and should be integrated into the drug quality program.
3. USP DQI, WHO, the National Laboratory for Drug Quality Control (NLDQC) , and the National Malaria Center could collaborate in conducting an antimalarial drug quality survey to determine the relationship of drug quality to drug resistance. This study will not require

major investment. USP will design the sampling and testing procedures in collaboration with the NCL, and purchase the drugs and reagents. WHO will arrange for drug collection from high-risk and border areas. NLDQC will conduct the drug analysis. This study will also raise awareness among other Mekong countries. It was clear from the discussions at the ACTMalaria meeting (April 20-24, 2002, Malaysia) that drug quality is still perceived as a minor issue within the RBM program in the Mekong.

4. USP should visit the Cambodia Pharmaceutical Enterprise and assess their GMP improvement, before they start any production but after they finish the stability and bioavailability studies. WHO and all local authorities are requesting USP DQI's assistance with this.
5. USP should work with Hollykin, the Chinese company that plans to manufacture Artekin™ (dihydroartemisinin + piperaquine) in Cambodia, to ensure that the factory GMPs are acceptable.

USP DQI
Sentinel Surveillance Site Assessment
Viet Nam, May 1-5, 2002

General Background

Viet Nam is situated in eastern Indochina with a population of about 80 million. The country covers an area of 330,941 km² with a population density of 234/ km². Viet Nam is bordered on the west by Laos and Cambodia, and on the north by the Yunnan and Guangxi Zhuang provinces of China. The average annual population growth in Viet Nam is about 1.5%, with 20-25% of the population living in urban areas. Less than 6% of the Vietnamese population is above 64 years of age. Among the six Mekong Delta countries I visited, Viet Nam has one of the highest human development and gross domestic product (GDP) indexes (after China and Thailand), and almost the highest education index in the region. The GDP per capita is about \$2,000 U.S. in Vietnam, distributed to services (45%), industry (30%) and agriculture (25%). Viet Nam has one of the highest life expectancy rates and the lowest infant mortality rate in the Mekong region.

Vietnamese Malaria Control Program

Viet Nam is subdivided into 61 provinces; each province is subdivided into districts; and the districts are made up of communes. There are two border sentinel sites: Lai Chau, in the north and Khan Hoa in the south. Since 1991, Viet Nam has operated the National Malaria Control Project (NMCP), a strong vertical system which has provided the core for integrating malaria control into the health system network from the central to the furthest decentralized levels with a good implementation of WHO guidelines. The first objective of the NMCP is to reduce mortality at all levels, but especially at the grass-roots, by early and prompt diagnosis and treatment, by providing sufficient anti-malarial drugs for treatment and prophylaxis, and by promoting rational and safe use of anti-malarial drugs.

The National Institute for Malariology, Parasitology, and Entomology (NIMPE) is the working group of the NMCP board that is in charge of the malaria control program and all planning and implementation of NMCP guidelines. NIMPE and sub-NIMPE staffs are in charge of data collection, drug resistance monitoring, drug management and distribution, and follow-up of the malaria control program implementation.

Visit to the National Institute of Malariology, Parasitology, and Entomology (NIMPE), May 2

Participants: Dr. Le Xuan Hung, Director of Epidemiology
Dr. Doan Hanh Nhan, Vice Director
Dr. Nguyen Manh Hung, Deputy Director
Dr. Abdelkrim Smine, USP DQI

Unable to attend: Dr. Le Dinh Cong, Director, Roll Back Malaria (RBM) program, whom I met at the ACT Malaria meeting in Malaysia, was out of the country.

Dr. Doan Hanh directed a tour of the institute and described the malaria control program in Vietnam. A malaria eradication program, started in 1958 in North Vietnam, reduced the slide positive rate (SPR) 20 times over the next six years. During the war (1965-1975), however, the

malaria situation fluctuated. After the country was reunified in 1975, the malaria eradication program was expanded to include the whole country. By 1980, the SPR in the south was 2.9%, down from 11.7% in 1976. The RBM program was being well implemented and the actual malaria situation is a lot different from the past.

Recent data indicate that in the year 2001, there were 234,491 malaria cases in Vietnam; of the 792 severe cases, only 81 patients died of malaria, compared to 4,641 deaths in 1991. In the same year, 63,041 of 234,491 were positive malaria cases; 47,051 cases were caused by *Plasmodium falciparum* (about 76%); and 15,127 cases were caused by *Plasmodium vivax* (about 24%).

Treatment guidelines

Therapeutic drugs:

The national treatment guideline is reviewed each year for malaria control and is enforced in both public and private sectors. The list of first line drugs contains chloroquine, mefloquine, artemisinin, artesunate, primaquine, quinine and sulfadoxine-pyrimethamine, and drug combinations. The treatment depends on the severity of the malaria and on the parasite causing it. The recent data from NIMPE showed that in 2001, 75% of malaria cases were *Plasmodium falciparum* type and 25% were *Plasmodium vivax* type. Chloroquine is still efficient against *P. vivax*, while *P. falciparum* cases are treated with a combination of artesunate and mefloquine.

Prevention measures:

People at high risk for malaria receive a preventive treatment with chloroquine, mefloquine, and sulfadoxine-pyrimethamine. In addition to prophylaxis, a vector control program has been followed for the last ten years. Sixty to eighty percent of the population lives in high-risk areas, which are protected by insecticides; bed nets are distributed free of charge to the poor. NIMPE monitors the vector distribution and the effectiveness of insecticides.

Diagnosis of malaria:

Blood smears seem to be the most often used tool for diagnosis. NMCP provided 2800 microscopes to all health facilities in the commune, district, and province levels, and plan to extend this service to villages. Dipsticks are used as a quick diagnosis tool, but they seem not to be effective all time.

Drug distribution:

Each year the NMCP studies the needs of the entire country. The drugs are distributed accordingly to all provinces twice a year. In some provinces, the NMCP provides the money and the provincial managers buy the needed drugs; but all anti-malarial drugs are supplied free of charge.

Data reporting network:

NIMPE collects all data relating to malaria. This includes outbreak cases, malaria cases, type of parasite, drug resistance, and drug management. In our trip to the NIMPE, we saw data from all over the country, current up to the past two weeks.

Visit to the National Institute of Drug Quality Control (NIDQC), May 2

Participants: Dr. Nguyen Manh Hung, Deputy Director, NIMPE
Dr. Le Xuan Hung, Director of Epidemiology, NIMPE
Dr. Trinh Van Quy, Director, Associate Professor NIDQC
Dr. Trinh Van Lau, Vice Director, NIDQC
Dr. Nguyen Trong Luu, head of Planning Dept., NIDQC
Dr. Abdelkrim Smine, USP DQI

The Director of the Institute introduced the participants and presented an overview of the Institute's background and activities. The NIDQC was created in 1971, supervised by the Ministry of Health (MoH). The NIDQC represents the highest body in the country for determination of drug quality. NIDQC is a key component in the governmental management of pharmaceuticals in Vietnam, including the drug department, quality control, and drug inspection.

The Institute receives a yearly budget from the MoH, in addition to some money for the drug analysis connected with registration. It is housed in two large buildings of three stories each, one new, and one older but undergoing renovation. This site employs 130 working staff; another "sub-Institute" of drug quality control in Ho Chi Minh City employs 90 staff members. The Vietnamese pharmacopeia commission maintains its offices in the in Ho Chi Minh City facility.

Duties of the NIDQC

The NIDQC is charged with the responsibility to:

- Determine and control the quality of drugs, including raw materials and finished drug substances, manufactured within the country or imported. Before the MoH will register a drug, the lab does all required drug analysis; it also assures the post-marketing surveillance of drugs.
- Determine the specifications for monographs to be compiled in the Vietnamese Pharmacopeia.
- Establish, produce, and provide reference standards.
- Monitor the quality of all kinds of drugs for humans sold in the Vietnamese market.
- Provide technical assistance and support to provincial drug quality control units.

According to the Institute's activity report, it alone checks the quality of an estimated average of 3,000 samples each year. The drug quality laboratories throughout the country check a total of 40,000 samples every year. The NIDQC so far has established 50 national reference standards and hundreds of working standards used in drug quality control in Vietnam. The Director said that the major achievement of the Institute was the elimination of counterfeit drugs from the Vietnamese marketplace. In 1991, about 7% of the drugs were fake; in the past four years this number was kept under 0.5%. Of the more than 10,000 drugs registered in the Vietnam, about 100 substandard drugs are still detected per year and are reported to the MoH.

The Institute uses the British, Chinese, and Japanese pharmacopeias, and maintains a copy of USP24-NF19. They said they use USP reference standards and monographs, but

complain about the cost of USP products. They were unaware that USP has a distribution site in Asia.

The Director gave me a new edition of the Vietnamese Pharmacopeia as a gift and said that the Institute would be very interested in collaborating with USP on any project; in fact, we discussed the idea of developing International Reference Standards for artesunate and its derivatives. The Director said he is willing to work with us, especially since his Institute has developed high quality standards for artesunates, samples of which he showed me packaged in glass sealed tubes for single use.

Visits to the Labs

The Vietnamese laboratories are well equipped and fully functional. They contain separate units, such as physico-chemical, biological, microbiology, and traditional medicines. On our visits we saw instruments for UV-VIS, IR, FTIR, and GC-MS, as well as amino acid analyzers, dissolution systems, TLC equipment, and titration equipment. The labs appear to conduct almost all tests for drug analysis including sterility tests, microbial contamination, pyrogen and irritation tests, LD₅₀ and more.

While we did not inspect the labs in detail, those we visited seemed to utilize good practices. The equipment appeared to be well maintained; the date of services, the manuals, and the SOPs are posted close by. The reagents are well stored in a separate room and the microbiology lab is a restricted area. In each division, the lab chiefs we talked with were very knowledgeable about pharmacopeial testing.

Visit to Mediplantex Pharmaceutical Company, Hanoi, May 3

Participants: Dr. Le Xuan Hung, Director of Epidemiology, NIMPE
Dr. Tran Binh Duyen, Director
Mr. Nguyen Cong Binh, Deputy Manager
Dr. Le Vien, Chief, QA & QC Department
Dr. Abdelkrim Smine, USP DQI

Mediplantex is the number one national medicinal plant company. Founded in 1971, it is a licensed manufacturer of pharmaceuticals and allied products. Mediplantex are traders: Importers and exporters of pharmaceutical products, traditional medicines, pharmaceutical raw material and packaging, medicinal herbs, cosmetics, essential oils and other goods. We were not invited to visit the production plant, so all information given here is what the staff presented to us.

Mediplantex prides itself on the superior quality of its products, and gave us a list of those manufactured in the plant. Mediplantex makes the anti-malarial drugs artemisinin, artesunate, and artemether tablets; it also produces chloroquine, mefloquine and quinine tablets. Mediplantex provides the needed anti-malarial drugs to Vietnam, but it also does trade many other countries. According to the Director, the company complies with the Vietnamese GMP, and continues to improve manufacturing at all levels. Mediplantex products are certified in many countries including Japan, Belgium, Germany, and Australia. The company currently is considering starting a new line of drug combinations.

We also discussed the drug market in Africa and the need for the production of high quality drugs. The Director said that Mediplantex controls artesunate production from plant to finished product, and seems confident that his products are of a good quality.

Visit to the Quality Control Laboratory, May 3

Mediplantex's Quality Control Lab is far from meeting GMP. They have most of the basic equipment for drug testing; they have a modern microbiology lab, HPLC, dissolution tester, spectrophotometers, and some basic equipment for physico-chemical tests; they have the last edition of the BP on CD-Rom, and photocopies of the USP-NF in three parts. We didn't have the time to check in detail, but we believe that the lab needs a great deal of improvement. Mediplantex needs to have a GMP-qualified QC lab before they can claim that all of its products are made under GMP guidelines. The lab chief said that they are working to develop an HPLC procedure for artesunate using derivatization method. Being very interested myself in developing such a method to be used for an international monograph for artesunates, I got a reprint of a paper from Australia about this method.

Visit to the Sentinel Surveillance Site, Lai Chau Province, May 3-5

Lai Chau Province is located in the northwestern region of Vietnam, bordered by China to the north and Laos to the west. Lai Chau is the second largest province in the country with about 70,000 km² of land and a population of over 600,000. The Malaria Control Center and the provincial hospital are located in Dien Bien Phu City. This is an historical area, as it was in this valley that the Vietnamese won the battle of independence from French colonization on May 7, 1954.

Visit to the Malaria Control Center, May 3

Participants: Dr. Nguyen Van Linh, Director, Malaria Control Center (MCC) of Lai Chau
Dr. Nguyen Van Doi, Vice Director, MCC
Dr. Phan Van Luyen, Director of Health Service, Provincial Health Service (PHS)
Mr. Phan Ngoc Quynh, Director, Drug Quality Control Center (DQCC)
Ms. Xin, Vice Director, DQCC
Dr. Le Xuan Hung, Director of Epidemiology, NIMPE
Dr. Abdelkrim Smine, USP DQI

The Director gave us an overview of the Center's activities and the malaria management program. Lai Chau Province is considered a high priority in terms of malaria control. There has been an increase of malaria cases in the area due to the population movement: People from this province move between borders and also to the central area of the country for economical reasons. Agriculture and commerce support the main economy of the province. Farmers from Lai Chau work in coffee plantations in border areas in the south or in the mountains. The population of the province is comprised of minorities.

The Vietnamese and the Laos armies collaborate to control malaria and other communicable diseases. The malaria control center is in charge of implementing the national malaria control program and of anti-malarial drug distribution to the entire province, which includes 10 districts and 2 towns. The center also collects all data on epidemiologics, drug

resistance, and effectiveness of the prevention program. The private sector is almost non-existent in Lai Chau.

Treatment guidelines

Therapeutic drugs:

- For *P. falciparum* – about 60% of malaria cases in Lai Chau province – CV8, a combination drug made at Central Pharmaceutical Factory in Ho Chi Minh City that contains dihydroartemisinin (32 mg), piperaquine (320 mg), primaquine phosphate (5 mg) and trimethoprin (90mg) [One CV8 regimen for adults is 8 tablets (3 days).]; mefloquine; and sulfadoxine pyrimethamine.
- For *P. vivax* – about 40% of malaria cases in Lai Chau province – chloroquine is still effective and is used for treatment.

All anti-malarial drugs are given to patients free of charge. There is a budget of 200-250 million Viet Nam Dong per year allocated to Lai Chau for anti-malarial drugs, enough to cover all the province needs. The budget is reviewed each year, and the drugs are provided by NIMPE to all provinces twice a year.

Prevention Measures:

Populations living in high-risk areas are given chloroquine and sulfadoxine pyrimethamine. The Director said that, last year, 400,000 spray and bed nets were distributed throughout the province. While visiting the city market, we noticed that almost all shops that sell clothes also sell bed nets. These bed nets are made in Vietnam. The prevention program covers an estimated 30% of rural areas in Lai Chau.

Drug Resistance:

The Malaria Control Center also monitors drug resistance and drug efficacy in the province, which are evaluated regularly by NIMPE staff. According to the Director, only 12.3% resistance to chloroquine (*P. vivax*) was found last year; for resistance to artesunate, no data are yet available.

Diagnosis of Malaria:

Mainly diagnosed by blood smears, quick checks are also performed with dipsticks purchased from India. There are a total of 30 microscopes in the province and the center is trying to get 10 more. All district health centers have microscopes, as do two-thirds of the commune health centers. The military hospitals are also incorporated into the malaria control program to cover the army and the civilians in the area.

Visit to the Drug Quality Control Laboratory, May 4

The Quality Control Laboratory has four rooms and 12 staff workers, eight of whom are trained pharmacists. The Laboratory's primary function is to check the quality of different drugs on the market in Lai Chau province. The Director said that the anti-malarial drugs are checked four to five times a year. The Lab does the drug testing for the Malaria Control Center and for the lower health centers. After each anti-malarial drug control, the Lab reports the results to the

Malaria Center, which in turn reports them to NIMPE. The Laboratory has a yearly budget of 50 million VND.

While visiting the Laboratory, we observed that it has the basic equipment: One HPLC, a new spectrophotometer, a small dissolution tester (single-tablet tester), TLC equipment, reagents, centrifuges, refrigerator, incubators, and other equipment for physico-chemical testing. The Laboratory seems to use the British Vietnamese Pharmacopeias; the USP-NF was not in sight. The Laboratory has computers and access to internet.

The Director complained that, on his limited budget, one of the major problems they experience is difficulty controlling the Laboratory's inside environment. At times, they are unable to run experiments because the high heat and humidity will affect the data.

This is the first time that I found a quality control unit at the sentinel site level. Clearly, the Lab cannot perform all Pharmacopeial tests, but it can complete many more than we expected. They already perform TLC on a regular basis, so what I think would benefit this province—in fact, the whole malaria control program—is for USP DQI to provide a short training on GMP guidelines and how USP carries out quality drug tests.

Visit to a Hospital, May 4

Participants: Dr. Nguyen Van Linh, Director of the Malaria Control Center (MCC) of Lai Chau
Dr. Chau, Director- Professor of the provincial hospital
Dr. Cong, Director of Communicable Diseases Department
Dr. Le Xuan Hung, Director of Epidemiology, NIMPE
Dr. Abdelkrim Smine, USP DQI

Even though the Malaria Control Center is charged with overseeing all malaria program management, we wanted to talk with physicians to elicit their opinions. The hospital we visited had 240 beds. Malaria drugs and consultations are free-of-charge, in accordance with the malaria program guidelines. The Director gave us the latest data on the malaria cases in his hospital. From January–April 2002, there were 25 malaria cases, with only four confirmed by blood smears. He said that, in general, about 60% of the cases are *P. falciparum* and 40% are *P. vivax*; they do not see other Plasmodium types. Malaria represents about 2% of the total diseases they treat, while all communicable diseases represent about 9% of total diseases in this hospital.

Visit to a Private Clinic, May 5

In this area there are very few small, private clinics which are usually run by doctors working in the public sector. At the small clinic we visited, the doctor said that they refer any patient with malaria symptoms to the public hospital; they do not have anti-malarial drugs available for treatment. When asked why, he said that the drugs are given free in the public hospital, so there is no need to carry them.

Visit to a Public and a Private Pharmacy, May 5

There is no apparent difference between the public and private pharmacies, other than the fact that the public pharmacy belongs to the government. Neither had anti-malarial drugs, and for the same reason: The drugs are given free in the hospital next door.

Visit to the City Market, May 5

In this country, it is illegal to sell drugs without a license. We did not see drugs of any kind in the market other than the traditional medicines and herbs. Bed nets, manufactured in Vietnam, were sold everywhere, though they were not insecticide-treated.

Dr. Smine paid a courtesy visit to Dr. Christoph Heuschkel, European Commission (EC), who was here for final evaluation of EC program in neighboring province. The EC will end its Malaria program in the Mekong by the end of this year.

Conclusion and Recommendations

In my opinion, Viet Nam has the best malaria management program among all the countries we visited. The government guidelines are strictly implemented at all levels. Our visit was given a high priority and everyone was fully cooperative and helpful.

As for setting up a drug quality system in sentinel sites, the Vietnamese are already doing what we want to encourage others countries to do. Where Viet Nam needs USP DQI help, however, is in the manufacturing of anti-malarial drugs. USP could introduce good manufacturing practices and drug analysis as it is performed in the United States. Based on my own observations and what I learned from WHO and EC staff here and in other countries, the Vietnamese are a very hard working people. Once they are shown something, they will duplicate it, and implement the program very well.

Of the two sentinel surveillance sites, the one I visited in Lai Chau and Khan Hoa in the south, Khan Hoa is purported to be more fully developed, because the province is richer. From what I learned from Allan, Dennis, Krongthong, and Stephan, WHO is eager to encourage the Vietnamese to comply with international GMP standards. With that in mind, I recommend gathering four staff leaders – one from the National Control Lab, one from the sub-Institute in Ho Chi Minh City, and the directors of both the Lai Chau and Khan Hoa provinces – to visit USP for a weeklong training. Once they have observed how U.S. labs follow GMP, we can urge WHO to approach the appropriate official in Vietnam's Ministry of Health to upgrade their labs and manufacturing plants to meet international GMP standards.

Sentinel Surveillance Site Assessment Thailand, May 5-11, 2002

General background

Thailand covers an area of 518,606 km² and has an estimated population of 61,900,000. The country is bordered by Myanmar on the west and northwest, by Laos on the east and northeast, and by Cambodia on the southeast. The country is divided into 76 provinces, which are divided into districts, subdistricts, and villages. About 70% of the population lives in the rural areas; the urban population is concentrated in Bangkok and neighboring provinces.

Thailand has the highest human development index among the six Mekong countries. The Thai Gross Domestic Product (GDP), about \$7,000 US per capita, is the highest in the Mekong region and is distributed among services (50%), industry (40%), and agriculture (10 %). Thailand has one of the highest life expectancy and the lowest infant mortality rates in the Mekong region.

Visit to Malaria Division, Ministry of Health, May 7

Participants: Dr. Abdelkrim Smine, Research Scientist, USP DQI
Dr. Krongthong Thimasarn, WHO Roll Back Malaria Regional Director
Mrs. Soavanit Vichaikhanka, Technical Officer 8, Department of Communicable Disease Control, Ministry of Health

Mrs. Soavanit presented information on Thailand's malaria control program and the actual malaria situation in the country. Malaria is still a major health risk in Thailand. In 1949, malaria caused 201.5 deaths per 100,000 population; today, because of the malaria control program in Thailand, there is only about one death per 100,000 population. But there were a total of 149,586 microscopically confirmed malaria cases in Thailand in the year 2000. Of these cases, 61.3% were Thai nationals; the rest were foreign national cases. Of the foreign national cases, 89% were found at the Thai-Myanmar border provinces.

Malaria in Thailand is related to forestation. The disease is prevalent around its international borders, while malaria has been eradicated for more than two decades in the center of the country. *An. dirus* and *An. minimus* are the principal vectors, and the parasites commonly found are *P. falciparum* (51%), *P. vivax* (48%), and *P. malriae* (1%).

The Thai malaria control program manages 537 clinics, health centers, and health posts throughout the country. In addition to the paid health workers, there are a total of 33,000 malaria volunteers, located mostly in remote areas. Malaria staffs at the local level are responsible for collecting blood slides from health centers and village volunteers, and tracking the malaria cases for adequate treatment.

Treatment guidelines

The malaria control program stratifies areas of the country into three levels, based upon their vector sensitivity to mefloquine:

- Non- or low mefloquine-resistant areas
First line drug: Mefloquine 750 mg + primaquine 30 mg - single dose
Second line: Quinine + tetracycline for 7 days, or quinine alone for 7 days
Third line: Artesunate or artemether 700 mg in divided doses over 5 days + primaquine 30 mg on the last day
- Moderate mefloquine-resistant areas
First line drug: Mefloquine 750 mg, followed by artesunate or artemether 300 mg at 6-hour intervals on day one; artesunate or artemether 700 mg on day two
Second line: Same as non/low mefloquine-resistant area guidelines
Third line: Same as non/low mefloquine-resistant area guidelines
- High mefloquine-resistant areas
First line drug: Day 1 – Mefloquine 750 mg, followed by artesunate or artemether 300 mg + mefloquine 500 mg 6 hours later
Day 2 – Artesunate or artemether 300 mg and primaquine 30 mg.
Second line: Same as non/low mefloquine-resistant area guidelines
Third line: Same as non/low mefloquine-resistant area guidelines

Treatment of *P. vivax* and *P. ovale*

- Chloroquine 1500 mg over 3 days
- Primaquine 15 mg daily for 14 days

Treatment of *P. malariae*

- Chloroquine 1500 mg over 3 days

Treatment of mixed infections

- If mixed with *P. falciparum* malaria, treat as *P. falciparum* according to the degree of resistance to mefloquine as indicated above

Presumptive treatment and chemoprophylaxis

The presumptive treatment, using sulfadoxine-pyrimethamine together with primaquine, was being given to symptomatic cases with suspected histories. The malaria control program decided to discontinue this treatment at the end of 2001 because of the risk of creating drug resistance.

Chemoprophylaxis is not recommended for the general population. Personal protection using mosquito repellents and impregnated bed nets (IBN) is strongly recommended. Daily doxycycline 100 mg for no longer than 3-4 weeks is recommended for all instances, in cases where chemoprophylaxis is unavoidable.

Vector control activities

In the year 2000, vector control activities covered a total of 3,371,185 people using such methods as indoor residual spraying (IRS) with deltamethrin 5% WP, at a target dosage of 200 mg/m². Some of the population was protected under emergency conditions. In addition to IRS, biological control, source reduction, and personal protection with IBN were also used.

Current status of drug resistance

Recent studies on drug resistance at six Thai sites have shown that the combination of mefloquine and artesunate is still efficient to treat malaria (93% adequate clinical response). Resistance to mefloquine, however, has become significant in some areas, like Ranong (19% resistance in a 2000 study) and Mae Hong Son (12.2 % resistance in 1997 study). In the Kanchanaburi area, resistance to mefloquine decreased from 18% in 1997 to almost 0% in 1999. Additional studies are needed to confirm the drug resistance situation.

Visit to the Division of Drug Analysis, Ministry of Public Health, Bangkok, May 7

Objective

On November 19, 2001, a USP DQI team visited the Division of Drug Analysis (DDA) in Bangkok to evaluate the capabilities of this government laboratory and to assess their conformance with Good Manufacturing Practices (GMP) in the analytical testing of drug products. The DDA laboratory will be used by WHO as an international center for antimalarial drug analysis. This was a follow-up to assess the improvement made by this laboratory after USP DQI's first visit.

Scope

The scope of the evaluation covered major GMP systems relative to a quality control laboratory. We met with DDA staff, visited the laboratories, and reviewed samples of routine analytical and support documentation, such as worksheets, logs, and instrument maintenance and calibration records, for good laboratory practices.

Findings

The laboratory is able to conduct pharmacopeial drug analyses, and has the means to perform microbiological testing. The lab is also developing a molecular biology section. During our visit, we noticed that the lab is being used to its full capacity. It has basic analytical instruments including HPLCs, GC, and Atomic Absorption. DDA has adopted the USP as their official compendia.

The laboratory took corrective actions after USP DQI first visit. The oven used for LOD was repaired. Each piece of equipment has a sticker indicating the last and next dates of calibration. Staff training has been conducted in the lab, so we are told, though not all staff seem to apply what they were trained to do all of the time.

The major adverse finding is that current resources, both human and instrumentation, present capability limitations. The current backlog of nearly 700 samples has not changed in number since USP DQI's first visit, despite that fact that all available equipment is being used to

capacity. Due to the economical situation in the country, the DDA has a very limited budget and there is an obvious shortage of qualified personnel to keep up with the high demand.

A few GMP deviations were found during our visit to the lab facilities:

- Some solutions were stored without labels.
- One nitrogen tank was unsecured.
- HPLC waste was not labeled.
- Glass bottles were stored inappropriately.
- One equipment maintenance log was not well updated.

All these deviations can be corrected easily and do not affect the workflow or the accuracy of the data produced in the lab. In fact, when these deviations were discovered, laboratory management acknowledged that they should not have occurred, and we later noticed that corrective actions had been taken. These points are indicative of the need for in-house training on basic good laboratory practices, however. Many official operating procedures still need to be issued and implemented.

Overall Recommendations

The laboratory has made a significant improvement and we believe that DDA has the potential to supply a satisfactory analytical testing service for WHO. There are, however, human and instrumentation resource limitations that first need to be addressed. To increase the efficiency and throughput of the lab, we recommend that WHO arrange assistance for DDA to hire additional lab staff (two-three pharmacists) and add new instrumentation (at least two HPLCs). Without this support, it is unlikely that DDA will be able to analyze all the antimalarial drugs available in the region. USP DQI believes that, at this time, the DDA laboratory needs technical assistance to establish some standard operating procedures, to put together some laboratory practices, and to provide a short external training on GMP drug testing for a few staff.

Visit to Chon Buri Regional Medical Sciences Center, May 8

Drs. Smine and Thimasarn met with the Center's director and the lab chiefs of the drug analysis section. After about an hour's discussion, they visited the laboratories.

The Regional Medical Sciences Center of Chon Buri was established in 1983 as one of the 24 divisions of the Department of Medical Sciences, Ministry of Public Health. It is the technological center of seven provinces on the eastern seaboard of Thailand and the regional facility for food and drugs analysis. The Center employs a total of 55 employees: 12 scientists in the Drug Section (5 pharmacists, 2 medical scientists, and 5 technical staff, 9 scientists in the food section, and 7 scientists in the clinical pathology section. The major activities of this Center include:

- Analysis of public health products: pharmaceuticals, food, cosmetics, radioactive equipment and medical devices;
- Analysis of food and water products quality for registration purposes;
- Determination of narcotic and psychotropic substances;
- Support surveillance of certain diseases;
- Forensic, occupational health, and environmental sciences;

- Thai Herbal Medicine certification program; and
- Distribution of information and technological knowledge in medical sciences.

The Chon Buri Medical Center is also responsible for testing the drugs collected by drug inspectors from the general and district hospitals in the eastern part of Thailand to ensure their efficacy and safety.

Built in 1987, the Center's laboratories are large and modern. They have all the basic equipment needed for drug analysis and all of the required tests for antimalarial drugs could be performed in this facility. The Chon Buri Center would also be the best facility to train district staff on antimalarial drugs testing. One drawback, however: the laboratory staff of the drug section seems to lack the knowledge of many basic laboratory practices that are critical to ensure good quality data. Training the laboratory staff on good laboratory practices, together with technical assistance, would greatly increase the performance of this laboratory.

Chantaburi Province, Sentinel Surveillance Site/Cambodia Border

Visit to Center of Vector Born Diseases, May 8

This Center is responsible for all aspects of communicable diseases in Chantaburi Province. The Director and the Vice Director of this Center accompanied us on our tour here and on our visits to all other malaria facilities in the region. Malaria centers, such as this one, manage malaria patients' treatment. The Center of Vector Born Diseases is the provincial office for all district malaria centers. It provides the drugs, the equipment, and the reagents needed for blood smears. Data about malaria cases, vector type, patient background, and disease history are collected here monthly, then processed and sent to the Malaria Division in Bangkok.

Visit to Phrapokjlao Chanthaburi Hospital, May 8

A mix-up in the scheduling prevented us from talking with doctors from the vector born diseases department, who were attending a daylong meeting. We spoke instead to the chief of the pharmacy department who said that only about 5% of malaria patients come to this hospital; 95% go to malaria centers to seek treatment. Because this is a public hospital, the use of artesunate plus mefloquine is allowed, upon CDC authorization. The list of antimalarial drugs stocked by the hospital pharmacy contains all the drugs in the Thai treatment guidelines, including artesunate 50 mg tablets and artesunate 60 mg injection. According to the pharmacy department, about 700 samples from all the drugs used in the hospital are sent each year to the Drug Analysis Division in Bangkok for testing. No fake drugs have been found in this hospital.

Visit to Pong Num Ron District Hospital, May 8

Pong Num Ron Hospital is the sentinel site for Chanthaburi Province and is attached to a malaria center unit. This hospital monitors drug resistance, one of only three sentinel sites where the Ministry of Health asks the hospital to perform drug resistance monitoring for the malaria control program. All other drug resistance monitoring is done in the malaria centers around the country. The hospital receives financial support from the Ministry to carry this task.

This site is located only 40 km from the Cambodian border in a forested mountain area, populated mainly by farmers. The malaria control program considers this site and the southern border province of Trat high-resistance areas. The malaria incidence is still high in these areas because of their proximity to the border. Malaria patients often come from Cambodia to seek treatment in Thailand because they believe that the quality of the drugs and the health care system are better than what they have at home.

Treatment guidelines

First line drug for *P. falciparum*: Mefloquine 1250 mg (split into 750 mg and 500 mg doses)+ artesunate 600 mg + primaquine 30 mg

Malaria in the province

This site treats about 1500 malaria cases per year, about 50% *P. falciparum* and 50% *P. vivax* types. Diagnosis in the hospital, in the malaria center, and in many villages is made by blood smears. Severe malaria cases are treated in the hospital while most cases are treated in the malaria center attached to the hospital.

The malaria center manages all aspects of the malaria control program in this district. The laboratory of the hospital is well equipped to carry out antimalarial drug quality control using TLC: nice benches, reagents, microscopes, three centrifuges, a refrigerator, and ovens. Three well-trained staff run the laboratory. The malaria center could also be used for antimalarial drug quality control, but more equipment would be needed. Since the two facilities are located in the same place and the hospital already monitors drug resistance, drug quality control should also be carried out in the hospital.

Visit to Ban Klam Village Hospital in Pong Num Ron District, May 9

This small village hospital, run by a single doctor, is located just a few minutes' walk from the Cambodian border. Diagnosis is made by blood smears and treatment is provided free for malaria-positive patients. Severe malaria cases are sent to the district hospital, about 30 km away. Most of the patients come from Cambodia. The doctor sees 5-10 patients with malaria symptoms daily and, on average, one or two are confirmed positive with blood smears. Data on the number of nationals or foreign cases, together with the vector type and disease history, are reported to the district malaria center.

Ban Klam Village Hospital receives all antimalarial drugs from the malaria program, and is very close to the district malaria center. This hospital need not be considered for drug quality control; however, the hospital's doctor could participate by sending samples of all antimalarial drugs brought in by patients to the Malaria Center for quality control. Because this border crossing area is very busy, this could prove an excellent site for drug information and drug quality issues, as information would travel across two countries in this high-risk area.

Kanchanburi Province, Sentinel Surveillance Site, Myanmar Border

Visit to Vector Borne Diseases Control Center, May 10

The Vector Born Diseases Control Center manages the malaria control program for Kanchanburi Province and serves as a sentinel surveillance site. The province covers a large area

(19,486 km²), which includes 872 villages, 27 municipalities, and 13 districts, and supports a population of 767,224. The rainy season occurs between July-October in this area. Most of this province is forested mountains that are crossed by three main rivers, Mae-klong, Kvey-Yai, and Kvey-noi. The majority of the population make their living from agriculture, such as farming and fishery. The road system is very good except in some of the more remote mountain areas.

Kanchanburi province is considered a low-risk area and, consistent with the treatment guidelines, the first line drugs used is mefloquine 750 mg + primaquine 30 mg in a single dose. Drug resistance is monitored by Songkhlaburi district hospital, close to the Myanmar border. In 2001, of the 151,199 blood exams performed in this province, a total of 7,394 positive cases were found. Of that malaria-positive total, 4164 were *P. falciparum*, 3190 were *P. vivax*, and the rest were either *P. malariae* or mixed types. The current malaria death rate is 0.04 per 100,000 inhabitants; it was 6.55 per 100,000 in 2000, and 13.31 per 100,000 in 1999. This indicates a huge drop in the malaria death rate over the last three years. While malaria cases are reported throughout the year, the high-risk period coincides with the hot and rainy seasons between April and August.

Visit to Christian River Khawai Missionary Hospital, Songkhlaburi District, May10

Participants: Dr. Abdelkrim Smine, USP DQI
Mrs. Soavanit Vichaikhanka, MoH
Ms. Duangoleun, Epidemiology Dept. Center office, VBDCC, Kanchanaburi
Mr. Sukit, Songkhlaburi Zone Chief

Songkhlaburi District is 130 km from Kanchanaburi City and 380 km from Bangkok. The area is all mountains and forest, but the roads are very good. The Christian River Khawai Missionary Hospital is a Christian charity hospital located about 30 km from the Myanmar border, very close to a Burmese refugee camp. We talked with the hospital's chief doctor and his assistant about malaria aspects in general in this area. The main problem, according to the doctor, is the presence of a nearby market (Three Pagodas) that sells poor quality drugs, namely a single-dose packet containing various tablets of both drugs and vitamins.

The patients who use this hospital come from the refugee camp, from Myanmar, and from Thailand. The hospital charges patients for treatments, but patients who cannot afford it are still admitted to the hospital and treated for free. The hospital had a total of 342 positive malaria cases during 2000, and a total of 763 malaria cases in 2001. About 50% of the malaria cases are *P. falciparum*, 40% are *P. vivax*, and 10% are mixed infections.

The doctor we spoke with raised one important issue about the treatment guidelines in this province: Artesunate is supposed to be used as the first line drug in this province, but is sanctioned only in the public hospitals. He believes that treatment guideline should be changed, soon, and supported his argument by noting the increase of malaria cases in the last two years. The mission hospital uses artesunate regularly, however, even though the Ministry of Health has given no authorization.

This hospital would not be a suitable site for antimalarial drug quality control: First, because of its status and, second, because malaria and antimalarial drugs are not the hospital's primary concern. In addition, the malaria control program has sometimes experienced problems working with mission hospitals. It is important to note, though, that in this province, 21% of positive malaria cases and 59% of total malaria blood exams are reported by sources other than malaria centers or public hospitals. This illustrates how mission and private hospitals are still a major force behind the control of malaria, at least in this province.

Visit to Songkhlaburi Vector Born Disease Control Center, May 10

This small health center is operated by one doctor and seven government workers. Only one employee on the post is permanent; all others work in the field most of the time. The center sees about 15 patients a month because it is open to the public only on Mondays; most patients go to the Malaria Center in the district hospital nearby. The district hospital has 30 beds and a staff of four doctors. The district hospital serves a population of 30,000, 60% of which are foreign nationals.

This area faces a serious problem: An abundance of poor quality drugs that are sold in many places in the district. The chief of the malaria center has collected a few packets of these drugs, which may contain five to six tablets of different shapes and colors with absolutely no indication about their type, dosage, or expiration date. The malaria center uses the same drugs found in all the public facilities we visited, but for some reason – whether access or the illegal or refugee status of many district residents – people still use the drugs sold in the informal market. They will go to the hospital only when their malaria becomes severe.

This district very badly needs a drug quality surveillance program. Drug quality testing could be done in the malaria center or in the district hospital, once the staff is trained appropriately. It is also very important to introduce a drug quality information program that will educate people and, subsequently, reduce the use of the drugs from the informal market. There was very little informative material in any of the malaria centers we visited along the Cambodian and Myanmar borders.

Conclusions and Recommendations

1. We support using the Division of Drug Analysis as an international center for antimalarial drug control in Southeast Asia. Before that can take place, however, the DDA laboratory staff would need to be trained in good laboratory practices, and many standard operating procedures needed to meet GMP would have to be issued and implemented. The same would be true for the staffs from the regional medical science centers.
2. In both sentinel surveillance sites we visited, antimalarial drug quality control could be achieved at the district level.
3. A concentrated drug information campaign is needed in border areas.

4. WHO needs to audit some Thai manufacturers for the quality of the antimalarial drugs they are putting on the market. In addition, a random antimalarial drug quality study is needed in Thailand.

USP DQI
Sentinel Surveillance Site Assessment
Lao PDR, May 12-17, 2002

General background

Lao People's Democratic Republic (informally known as Laos) is a mostly agricultural, land-locked country on the Indochinese peninsula, surrounded by five neighboring countries: Thailand to the west, Vietnam to the east, Cambodia to the south, China to the north, and Myanmar to the northwest. Three-quarters of the country's total 229,962 km² area is mountainous and covered by forests. Its poor roads and minimal infrastructure make travel to and from remote villages extremely difficult, particularly during the wet season. Southern Laos, where the site we visited is located, is densely forested and receives more rainfall than the north.

The total population of Laos is about 5 million; about 85% of the people live in the rural perimeter of the country, primarily along the Mekong River. Laos has the lowest population density in Southeast Asia. The population of Laos is relatively young: Almost 55% are under the age of 19 and only 4% are over the age of 65. The overall crude mortality rate is 15 per 1000, while the infant mortality rate due to all causes is 104 per 1000. Life expectancy at birth is 52 years for females and 50 years for males.

Visit to the Center of Malariology, Parasitology and Entomology (CMPE), May 13

Participants: Dr. Abdelkrim Smine, USP DQI
Dr. Krongthong Thimasarn, WHO Medical Officer, Roll Back Malaria-Mekong
Dr. Eva-Maria Christopher, WHO Medical Officer for Communicable Diseases
Dr. Douangchanh Keoasa, Director General, Department of Hygiene & Prevention, CMPE
Dr. Samlane, Vice Director, CMPE
Head of Epidemiology, CMPE
Deputy-in-Charge of Malaria Treatment, CMPE
Deputy-in-Charge of Vector Control, CMPE
Dr. Vanthaloan, Deputy-in-Charge of Drug Resistance Monitoring, CMPE

Drs. Smine and Thimasarn presented background information about USP and USP DQI involvement in the Roll Back Malaria (RBM) program, the purpose of this trip, and a summary of our work in other Mekong countries. Dr. Samlane gave an overview of the Malaria program in Laos and reviewed our schedule of activities.

Administrative organization

There are five departments plus the cabinet of the ministry within the Laos Ministry of Public Health. The malaria program activities are managed by CMPE, which is under the Hygiene & Prevention Department, while all clinical malaria activities are under the Curative Department. The food and drug analysis center operates under the Food and Drug Department (FDD). The country is comprised of 18 provinces divided into districts, and then into villages.

The Laos malaria control program began in 1959, with the support of the World Health Organization (WHO), but it was interrupted in 1961 due to war. WHO reinstated the malaria eradication program in Laos in 1969. The Lao National Malaria Control Program took over anti-malarial control activities in 1976 and principally implemented three strategies: early detection and diagnosis, prompt treatment, and selective residual spraying. In 1999, after a national meeting on policies, coordination, and cooperation of the program, Laos published a national policy guideline book on malaria control.

Malaria in the country

Malaria is a predominant health burden affecting all 18 provinces of the country with varying degrees of severity. The disease is endemic, with a seasonal peak coinciding with the heaviest part of the rainy season (July and August). In the year 2001, there were 26,932 confirmed malaria cases in the country with 242 deaths. Of these cases, 96% were *P. falciparum* malaria. The real figures are much higher, however; because of the difficult access to remote villages, a large number of cases go undocumented. The malaria mortality rate in Laos is one of the highest among the Mekong countries, though there has been a continued decline over the last five years, from 12.2/100,000 in 1996 to 4.7/100,000 in 2001.

Treatment guidelines

First line drug: Chloroquine
Second line: Sulfadoxine-pyrimethamine
Third line: Quinine

Artesunates are recommended for use in specific cases under medical control, in hospitals only. The drugs are free-of-charge only in villages; in the district levels and above, patients have to pay for both the drug and the consultation (blood smear).

Laos is the only country, among those we visited, where artesunates are not in the treatment guidelines of the malaria control program. When we asked the reasoning behind this, we were told that, in Laos, there are not enough data available to justify the change of treatment policies. A study conducted in Attapeu province between August–October 2001, however, shows that *P. falciparum* is 45% resistant to chloroquine alone and 20% resistant to chloroquine in combination with sulfadoxine-pyrimethamine. Mefloquine, however, is still 100% efficient against *P. falciparum*. There is no chemoprophylaxis treatment supported by the Laos malaria control program. More studies about all aspects of malaria are still needed in this country.

Diagnosis

Malaria is confirmed by blood smears in all malaria centers at the province and district levels. Dipsticks are used in hospitals for quick checking, especially in intensive care units. In health centers where there is no microscope, patients are given chloroquine tablets for three days, based on standard criteria, to define suspected cases. Severe cases are referred to a higher treatment level.

Vector Control

Impregnated bed nets (IBN) are used in domiciles of the Lao Loum area, Lao Theung ethnic minority area, and areas with migrating mountains to valley areas. IBNs are the main

prophylactic of the Laos National Malaria Control Program (LNMCP). IBN are impregnated with Deltamethrin 1%, with the concentration of 20mg per square meter. The Institute of Malariology, Parasitology, and Entomology (IMPE) is in charge of the management and technical criteria regarding the use of IBN.

Data reporting

Laos has a data reporting system in place: IMPE is the central level that receives data from lower levels each month – The villages report to the district, the districts report to provinces, the provinces report to IMPE. These data report the number of malaria cases, positive cases, blood tests, and parasite type.

Visit to the Food and Drug Department (FDD)

Participating: Dr. Abdelkrim Smine, USP DQI

Dr. Krongthong Thimasarn, WHO Medical Officer, Roll Back Malaria-Mekong

Dr. Eva-Maria Christopher, WHO Medical Officer for Communicable Diseases

Dr. Vanthaloan, Center of Malariology, Parasitology and Entomology

Mr. Ot Manolin, Head of Division, FDD

Mr. Kamreang, FDD

In April 2000, the national assembly of Laos adopted a new drugs and medical products law, promulgated by the president of the state. This law determines the principles, rules, and measures for the administration of planting, raising, protecting, exploiting, producing, exporting, importing, distributing, possessing, and using drugs and medical products. The Food and Drug Department is in charge of making sure that the law is being well implemented. FDD is also involved in new drug registration; the FDD laboratory tests some, but not all, new registered drugs. FDD staff members supervise and work with local drug manufacturers to improve their ability to produce good quality drugs.

The Laos drug registration procedure started in 1992 and follows WHO drug registration guidelines. There are about 1300 drugs registered in Laos, but it seems that about 40% of the drugs in the marketplace are not registered. Of the approximately 2000 pharmacies in the country, only 60 of them are run by pharmacists, another 100 are run by pharmacist assistants or other health professionals, and the rest are run by someone without pharmacy training. There are three categories of drug stores. The drug quality is a big problem in the country because of the weak registration procedures, lack of trained pharmacists outside urban areas, lack of resources, drug smuggling from neighboring countries, poor quality of locally manufactured drugs, and import of more than 70 % of drugs from abroad.

Visit to the Food and Drug Department Laboratory (FDDL)

There is only one laboratory for food and drug testing in Laos; it was started in 1995 with the support of the Swedish International Development Agency (SIDA). Of the 39 staff members who work in this lab, only seven are trained pharmacists.

We met with the laboratory director and the lab chief of the physico-chemical unit. The FDDL uses the U.S., British, European, and Japanese Pharmacopeias and WHO/ASEAN

reference standards. Some of these standards are provided by WHO. The lab tests an average of 1,500 samples each year, about 50% food and 50% drugs, on a yearly budget of less than \$2,000.

We made a number of observations on how the FDDL could be improved:

- The laboratory needs glassware, equipment, reference standards, and good quality chemicals.
- The staff of this lab needs proper training to be able to perform all drug testing.
- Procurements of chemicals and equipment take a very long time. Because of the open tender procedures, everything the lab buys has to be paid by foreign currency. This also reduces the allocated budget even more.
- The equipment is old and not well maintained.
- When problems arise with equipment maintenance, it is sent to Thailand or Singapore for repair.
- The lab cannot afford to calibrate and validate equipment as necessary.
- The lab has some basic equipment, which was provided through the SIDA fund:
 - HPLC, no autosampler
 - 3-4 columns only
 - FTIR, non-functional
 - 1 spectrophotometer
 - mQ water system
 - 1 pH meter
 - Balances, but no microbalance
 - Dissolution tester (seemed non-functional)
 - Other basic equipment for drug testing.

Being the only lab of its kind in the country, the FDDL needs a great deal of support in term of training and resources. Strengthening this laboratory would have a big impact in the drug quality control system in Laos. We shared our opinion with the FDD director and suggested that the local manufacturers improve their manufacturing practices to assure a good quality of drugs.

Visit to the Mahosot Hospital, Vientiane, May 13

Mahosot is the largest hospital in the Laos; it receives funds from Wellcome Trust. Mahosot's infectious disease unit is also in charge of clinical malaria studies with the malaria control program.

Malaria is rare in Vientiane City; in fact, this hospital reported only 43 patients in 2001, more than 90% of which were *P.falciparum*. The head of the infectious disease unit would like the treatment guidelines for malaria to be changed. *P. falciparum* has proven resistant to Chloroquine and Sulfadoxine-pyrimethamine in many areas around the world.

At the time we visited Mahosot hospital, only one malaria patient was admitted. The diagnosis of malaria is determined by blood work, but the ICU sometimes uses dipsticks for quick checking. Since this city is not a high-risk malaria area, we didn't ask to visit the hospital labs or pharmacy.

Visit to Pakntum District Hospital, Ventiane Province, May 14

Pakntum District Hospital is about a one-hour drive from the City of Ventiane. It operates with 41 staff – 5 doctors, 24 nurses, plus lab technicians and administrative staff – and a capacity of 11 beds. The hospital has received 95 patients since January 2002, but only one patient tested positive for malaria. The hospital reports malaria cases to CMPE once a month.

The hospital buys malaria drugs with the money collected from patients. The consultation costs 3,000 kip (about \$ 0.30) and a full drug regimen costs 15,000 kip (about \$ 1.50). The same charges apply to all three malaria drugs, chloroquine, sulfadoxine-pyrimethamine (SP), and quinine.

We bought a few antimalarial samples from the Pakntum hospital. The drugs we found in its pharmacy were bought in vrac, that is, in lots of 1,000 non-packaged tablets, and are kept in a container with a label corresponding to another drug. The pharmacist has no record of drug origins or expiration dates; the dose was not written on the container; and some tablets showed the apparent traces of moisture, indicating that they were not well stored. Tablets from different origins/manufacturers were mixed in the same container and the tablets of SP had expired, but were still in use.

The Pakntum laboratory has the following equipment available: centrifuge, microscope, refrigerator, reagents, lab bench, running water, electricity, and telephone.

Visit to the Malaria Center, Savanakhet (Sentinel Surveillance Site), May 14

Participants: Dr. Abdelkrim Smine, USP DQI
Dr. Krongthong Thimasarn, WHO Medical Officer, Roll Back Malaria-Mekong
Dr. Vanthaloan, CMPE
Mr. Kamreang, FDD
Dr. Tiengkham Pongvongsa, Director, Malaria Center

Savanakhet Province is located in the south of Laos along the Mekong River, across from Thailand. The economy of Savanakhet is 85% agricultural, primarily rice and wood; it is the second richest province in Laos after Ventiane. The province is comprised of 15 districts. The road system is very modern so access to the districts is easy. The general population of Savanakhet Province numbers about 700,000 with a GDP about \$200 per person. The average incidence of confirmed malaria cases is about 10/1000; 85% of these cases are *P.falciparum* and 15% are *P. vivax* type.

The treatment guidelines in the province follow the CMPE, which includes a first line of chloroquine, SP, and quinine. Artesunate is used only in hospitals, under medical control. The sale of artesunate is prohibited in all pharmacies.

The prevention program consists of providing and promoting the use of impregnated bed nets (IBN) once a year, covering 80 % of the entire province; IBN are subsidized by the World Bank. In the province and district health facilities, antimalarial drugs are not given free-of-charge, as is the case in the villages. In each district there is a malaria nucleus which manages the malaria program at that level.

In 2001, there were 7,623 positive malaria cases in Savanakheth and 34 deaths. All malaria data were presented to us updated to March 2002. This Center reports data to CMPE once a month.

Visit to the facility

The Malaria Center was built in 1996 and serves as the hub of all malaria program activities in the province. There are 21 staff working in the Center: two medical doctors, four medical assistants, and 15 laboratory technicians. The laboratory consists of three large, modern rooms with modern lab benches. The Center has microscopes, refrigerator, distilled water, reagents, computers, telephones, and access to the internet. Because it contains conference and training rooms, the Malaria Center in Savanakheth functions as the training center for all the southern provinces. **It is very well suited for drug analysis once the training and needed equipment are provided.**

Visit to the Provincial Food and Drug Department, May 14, 2002

Participants: Dr. Abdelkrim Smine, USP DQI
Dr. Krongthong Thimasarn, WHO Medical Officer, Roll Back Malaria-Mekong
Dr. Vanthaloan, CMPE
Mr. Kamreang, FDD
Dr. Tiengkham Pongvongsa, Director, Malaria Center
Director, Provincial FDD, and one senior staff member

The main activity of the provincial FDD, under the authority of the Laos FDD, is to manage food and drugs in Savanakheth Province. There is also a unit of FDD in each district. There are 20 staff working in this center; eight of them hold a bachelor degree in pharmacy and are trained in drug inspection. The director explained that because of the lack of resources, this center works with health facilities, drug companies, and drug buyers to assure that the drugs they buy are registered. Drug inspectors collect samples once a year and send them to Vientiane for testing, since this center has no laboratory or equipment for food or drug testing. Apparently, a laboratory is under construction, but it will take years before it can start testing the quality of drugs.

There are four major drug companies in the province, but most of the drugs they deal with are imported from Thailand. The director expressed his concern with the quality of the drugs sold in the province, but feels helpless without the ability to check the quality. He cited numerous examples of times when the center had collected drugs from district pharmacies and sent them to Vientiane for testing, only to find that the drugs were fake. In many cases, he said, by the time they get the results back – because it sometimes takes several months to get the tests done – the fake lot has already been sold. Many of his staff with pharmacy backgrounds find work elsewhere due to the lack of resources and the frustration of not being able to do the work they were trained for; their jobs consist mostly of paperwork.

Visit to the Provincial Hospital, Savanakheth City, May 14

Participants: Dr. Abdelkrim Smine, USP DQI
Dr. Krongthong Thimasarn, WHO Medical Officer, Roll Back Malaria-Mekong
Dr. Vanthaloan, CMPE
Mr. Kamreang, FDD
Dr. Tiengkham Pongvongsa, Director, Malaria Center
Dr. Phokhan Phrasithideth, Professor and Director, Savanakheth City Hospital
Vice Director, Chief of the Infectious Diseases Unit and Chief of the Lab

The French, during their occupation of Laos, built this large, 160-bed hospital. With the support of The World Bank, the main hospital now is being remodeled and a new building has been built. The Savanakheth City Provincial Hospital treats an average of 300 positive malaria patients per year. In 2001, of the 302 positive cases, about 85% are *P. falciparum* type. Diagnosis normally is made using blood smears, but dipsticks (Diamed from Switzerland) are used for quick checks. Artesunate is not registered but may be used under controlled circumstances.

In the pharmacy, we found that the hospital uses artesunate injection (Guilin Pharmaceutical); the artesunate is stored in the dry form, with the buffer packaged in a separate vial. All the antimalarial drugs we found here looked good and were well stored. The hospital's new laboratory is modern and well equipped, with centrifuges, spectrophotometer, numerous microscopes, Humalysers, reagents, and other equipment for blood tests. This hospital could be used for antimalarial drug testing; however, the Malaria Center and/or the provincial FDD center should be in charge of drug quality testing at the province level in Savanakheth city.

The director seems unhappy with the malaria program treatment guidelines. Most of the patients prefer to medicate themselves and take artesunate before they go to public hospitals. He expressed an urgent need to introduce a drug quality control program in the Malaria program and other health programs as well. A recent study done by WHO showed that the majority of patients in Laos self-medicate themselves.

Visit to Phalanxai District Hospital, Savanakheth Province, May 15

The Phalanxai District Hospital is about 100 km from Savanakheth City. There is a public health office at the same site, operating under the Hygiene and Prevention Department of the Ministry of Health (MoH), which is in charge of malaria and other diseases. The six health staff members who run the public health office are responsible for managing the malaria program. Another ten health workers deal with the promotion, impregnation, and distribution of IBN in the district villages; the World Bank supports the IBN program.

The public health office also oversees malaria drug procurement. The Director said that he buys all drugs from companies located in Savanakheth City. The hospital uses Chloroquine, SP, Quinine, Artesunate, and Tetracycline. Malaria patients are treated in the hospital under the Curative Department of the MoH. The drugs are given free-of-charge in the villages, but a full regimen costs 50,000 kip (more than \$5), which seems more expensive than in other places.

Malaria patients are treated in the hospital under the Curative Department of the Ministry of Health. Malaria is the first cause of hospitalization in this district, followed by diarrhea. The hospital receives about 20 positive cases each month, but that figure increases during the rainy season. About 90% of malaria cases are *P. falciparum* and 10% *P. vivax* type. This district has one of the highest malaria incidences in the province: In the year 2000, there were more than 1200 malaria cases, 3 deaths, and an incidence level of 43/1000. The following year, this was reduced to 832 malaria cases, 2 deaths, and an incidence level of 29/1000.

Phalanexai hospital has 13 beds and a small lab with a binocular microscope; there are three lab technicians who perform blood smears. Of those we interviewed, neither the hospital staff, nor the public health office staff seemed to know very much about drug quality or the basic practices of handling pharmaceutical products.

We bought samples of anti-malaria drugs from this site and were very surprised when we saw the condition of the stock. Both the Chloroquine and Quinine tablets looked very bad. They had no expiration dates; there were different types of tablets in the one container, which suggests that they had different origins; the tablets were very different sizes; most tablets had gray-black spots, which suggests problems with moisture and bad storage. The Sulfadoxine-pyrimethamine had expired in January 2002. The artesunates were mixed: different lots, different years, most of them expired, some expired in January 2001. We also recognized blister packs of the fake artesunates, like those found in Cambodia. In the entire drug stock, only one box of Chloroquine, the type provided by the program, looked fine.

The Phalanexai site is used by CMPE for drug resistance monitoring and is supposed to be better than other sites. **It could be used for drug quality monitoring after training the staff and providing equipment.**

Visit To Various Drug Stores

In Laos, the pharmacies are classified into three categories, Grade I, II, and III. Grade I pharmacies are licensed to import and export pharmaceutical drugs locally and abroad. Officially, they are able to sell more than 100 different types of drugs. Grade II pharmacies are licensed to sell between 75-100 different types of drugs including injectables. Grade III pharmacies cannot sell more than 75 different types of drugs and are prohibited from selling injectables. We were told that these regulations are often not rigorously monitored or enforced.

It also seems that a large majority of drug store keepers have very little knowledge about the drugs that they sell. Still, we must acknowledge that this type of store plays an extremely important role in the provision of health care in this country.

We were told that some of the stores sell artesunates even though it is prohibited, but we found none on our excursion. That may have been coincidence, or because the drug inspector who was with us is well known in the area and the six of us were riding in an official WHO car. But we did not find any artesunate. What we did notice is that the majority of the drugs, antimalarial and otherwise, were made in Thailand and, on most of these drugs, there was no indication of an expiration date.

Conclusions and Recommendations

There is no drug quality control program in place in Laos and one is greatly needed, because the quality of drugs on the market is very poor.

Priority should be given to improving the Food and Drug Department Laboratory. This lab requires additional resources and broad-based training. The FDD staff would best benefit from learning how to perform drug testing using simple methods, so that they can serve as trainers to FDD staff in the provinces and districts. When drugs are found to be fake, then they should be sent to the FDD national laboratory for more tests.

The malaria program should use Thin-layer Chromatography (TLC) to check anti-malarial drugs at the sentinel site. FDD staff trained on sampling and drug testing should use the Malaria Center labs to perform TLC and other simple methods to analyze drugs. When drugs are suspected of being fake or when they fail initial TLC tests, then they should be sent to the FDD national laboratory for additional testing.

A drug quality information campaign, similar to Cambodia's, is badly needed in this country. It should target hospital directors and other health care professionals. Drug store keepers should be trained in the basic rules that apply to buying, handling, and storing drugs, drug quality issues, drug dosage, and expiration dating. A system of data sharing would prove most beneficial.

Health officials from the Ministry of Health already have asked USP to lend assistance to their local manufacturers in achieving GMPs. As a start, the Ministry plans to help at least three national factories improve their manufacturing practices this year.

Itinerary
Sentinel Surveillance Site Assessment
Yunnan Province, China, April 16-21, 2002

**Dr. Abdelkrim Smine, Research Scientist, U.S. Pharmacopoeia
and
Dr. Krongthong Thimasarn, WHO Medical Officer, RBM Mekong
Accompanied by two national officers:**

- 1. Dr. Li Huaxian, Chief of Administrative Office, YIPD, Simao**
- 2. Dr. Yang Hengling, Deputy Director, YIPD, Simao**

Tuesday, April 16, 2002	Arrive in Kunming at 1pm and meet with WHO staff at 4 pm during Mekong Basin Disease Surveillance Project conference
Wednesday, April 17, 2002	Leave Kunming and arrive in Jinghong at 5 p.m. Visit Jinghong Prefecture, meet Dr. Wang, Director and Dr. Dai, Deputy-Director of Xishuan Banna Prefecture Public Health Bureau - 5.30 p.m. Stay overnight in Jinghong
Thursday, April 18, 2002	Travel by car (Yunnan Institute of Parasitic Disease) to Mengla County Visits two village clinics (Modang and Longlin Village Clinics) Stay overnight in Mengla County
Friday, April 19, 2002	Visit Public Health Bureau, Mengla County Meet Dr. Yang, Director of Public Health Bureau, Mengla County Meet Dr. Jiang, Director of Antiepidemic station Visit Drug Surveillance Bureau and meet Dr. Yang Xueli, Pharmacist, Deputy Director, Drug Surveillance Bureau Visit Mengla County Hospital Visit one private drug store and one public drug store Visit one private clinic and one private hospital of 25 beds Visit one administrative village clinic of 4 beds Stay overnight in Mengla County
Saturday, April 20, 2002	Travel to Jinghong Visit Menglun Township Hospital Stay overnight in Jinghong
Sunday, April 21, 2002	Return to Kunming at 9.40 a.m.
Monday, April 22, 2002	Travel to Penang, Malaysia

Itinerary
Sentinel Surveillance Site Assessment
Cambodia, April 25-May 1, 2002

Tuesday, April 23, 2002

Wednesday, April 24, 2002

Thursday, April 25, 2002

Arrived at 12:15 from Penang, Malaysia.
Meeting with WHO staff (2-3 PM)
Visit to the National Drug Control laboratory

Friday, April 26, 2002

Travel from Phnom Penh to Battambang by air, Karim and Reiko
Visit to Hospital of Battambang
Visit to public pharmacy of Battambang hospital
Visit to private pharmacy
Visit to rural health centers
Visit to Poevlun operational district hospital
Poevlun Hospital pharmacy

Saturday, April 27, 2002

Visit to the City of Pailin.
Visit of provincial hospital of Pailin.
Visit to the hospital pharmacy
Visit to private illegal pharmacy

Monday, April 29, 2002

Meeting with health officials in malaria program, National Malaria Center
Meeting the department of drugs and food, Ministry of Health

Tuesday, April 30, 2002

Itinerary
Sentinel Surveillance Site Assessment
Vietnam, May 1-5, 2002

Wednesday, May 1, 2002

Thursday, May 2, 2002

Visit to the National Institute of Malariology, Parasitology, and Entomology
Visit to the National Institute of Drug Quality Control
Visit to Mediplantex Pharmaceutical Company, Hanoi
Visit to the Quality Control Laboratory

Friday, May 3, 2002

Visit to the Sentinel Site, Lai Chau Province
Visit to the Malaria Control Center

Saturday, May 4, 2002

Visit to the Drug Quality Control Laboratory
Visit to a Hospital

Sunday, May 5, 2002

Visit to a Private Clinic
Visit to a Public and a Private Pharmacy
Visit to the City Market

Itinerary Sentinel Surveillance Site Assessment **Thailand, May 5-11, 2002**

Sunday May 5, 2002	Arrive in Bangkok
Monday May 6, 2002	Meet with Dr. Krongthong Thimasarn, WHO RBM regional director
Tuesday May 7, 2002	Visit Malaria division (morning) Visit of Division of Drug Analysis, ministry of health (afternoon)
Wednesday May 8, 2002	Travel by car to Chonburi province Visit Chonburi Regional Medical Science Center Travel to Chanthaburi Province (sentinel site / Cambodia border) Visit Center of Vector Borne Diseases Visit Phrapokjlao Chanthaburi Hospital Visit Pong Num Ron Hospital Spend a night in Chanthaburi city
Thursday May 9, 2002	Visit Unit of Vector-borne Diseases Control and a village hospital at the Cambodian border Ban Clongyai, Ban Klam. Collect samples. Drive back to Bangkok
Friday May 10, 2002	Travel to Kanchanburi Province (sentinel site / Myanmar border) Visit center for Vector Borne Diseases Control Center (VBDCC) Visit Christian River Khawai Missionary Hospital Visit VBDCC unit in Songkhlaburi. Collect samples. Spend the night
Saturday May 11, 2002	Drive back to Bangkok

Itinerary
Sentinel Surveillance Site Assessment
Lao PDR, May 12-17, 2002

Sunday, May 12, 2002	Visit to the Center of Malariology, Parasitology and Entomology Visit to the Food and Drug Department Visit to the Food and Drug Department Laboratory
Monday, May 13, 2002	Visit to the Mahosot Hospital, Vientiane
Tuesday, May 14, 2002	Visit to Pakntum District Hospital, Vientiane Province Visit to WHO sentinel site, Savanakheth Visit to the Malaria Center Visit to the Provincial Food and Drug Department Visit to the Provincial Hospital, Savanakheth City
Wednesday, May 15, 2002	Visit to Phalanexai District Hospital, Savanakheth Province
Thursday, May 16, 2002	Return travel to U.S.
Friday, May 17, 2002	